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PATHOLOGY

GENERAL AND SPECIAL

FOR STUDENTS OF MEDICINE

BY

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PHILADELPHIA
P. BLAKISTON'S SON & CO.
1012, WALNUT STREET
1906

PRINTED BY ADLARD AND SON, LONDON AND DORKING, ENGLAND.

PREFACE.

However desirable it may be in theory that the student of medicine should possess a wide knowledge of pathology, it has to be remembered that the majority of medical students become medical practitioners who require only such knowledge of pathology as will aid them in the art of healing. Moreover, in the comparatively short time allotted for the wide range of subjects comprised within the medical curriculum, it is impossible to deal with pathology in its entirety.

I have therefore endeavoured, in this book, to detail the essentials of general and special pathology, such as seem to me to be required by the majority of medical students. No novelty is claimed in the arrangement of subjects or presentation of the matter. The question of arrangement of subjects is a difficult one, but since every pathological process is intimately associated with other processes, it has not appeared to me to be one of particular importance.

The illustrations have been limited to those of microscopical appearances. Black and white, or even coloured, illustrations do not, as a rule, give an adequate picture of macroscopic specimens, and these are more readily (and ought to be) studied by the student in the post-mortem room and museum. I have made free use of the various excellent text-books on the subject, and desire to express my acknowledgment to their authors, especially Hamilton's *Text-Book of Pathology,* Hektoen's and Riesman's *Text-Book of Pathology,* Lazarus-Barlow's *General Pathology* and *Pathological Anatomy and Histology,* Sidney Martin's *Manual of General Pathology,* and Ziegler's *Text-Book of Pathological Anatomy.*

I am indebted to my friends and colleagues Dr. Aldren Turner and Mr. G. Lenthal Cheatle for the loan of some of the specimens[1] reproduced, to Mr. J. E. Barnard for the photo-micrographs, and to Mr. Frank Stratton for the drawings.

KING'S COLLEGE, LONDON.
March, 1906.

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[1] Dr. Turner, those of Plates XXVI, XXVII, and XXVIII, and Mr. Cheatle those of Plates IV, VI, and VIII, and Fig. 10.

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METRIC WEIGHTS AND MEASURES AND THEIR ENGLISH EQUIVALENTS.

1 millimetre = 0·4 ($\frac{1}{25}$) inch.
25 millimetres = 1 inch.
1 centimetre = 0·39 inch.
2·5 centimetres = 1 inch.
5 centimetres = 2 inches.
10 centimetres = 4 inches.

1 gram = 15½ grains (15·432 grains).
4 grams = 1 drachm (apothecaries'), nearly.
28 grams = 1 ounce (avoirdupois), nearly.
1 kilogram = 2·2 pounds (avoirdupois).
0·5 kilogram = 1 pound (avoirdupois), nearly.

1 cubic centimetre = 16 minims, nearly (16·23 minims).
3½ cubic centimetres = 1 fluid drachm, nearly.
28 cubic centimetres = 1 fluid ounce, nearly.
568 cubic centimetres = 1 pint.
1 litre = 1¾ pints, or 35 fluid ounces, nearly.

PATHOLOGY

GENERAL AND SPECIAL

CHAPTER I.

INTRODUCTION—DEFINITION OF PATHOLOGY—DIVISIONS OF PATHOLOGY—HEALTH AND DISEASE—HEREDITY—MALFORMATIONS—DEATH—THE CAUSES OF DISEASE.

Pathology is that branch of medical science which deals with the problem of disease, its origin, nature, and terminations, and the disorders of function and alterations of structure which induce it and result from it.

The study of pathology may be classed under several subdivisions—(1) morbid or pathological anatomy, which deals with the gross, naked-eye changes that occur in disease, and their distribution, *e. g.* the large heart of certain forms of heart-disease, and the small, rough, hard liver of hepatic cirrhosis; (2) morbid or pathological histology, which deals with the minute microscopical changes that occur in disease, *e. g.* the shrunken and fatty cells and the bands of fibrous tissue in the liver in hepatic cirrhosis; (3) general or experimental pathology, which studies the deviations from the normal of the functions of the organism in disease. In the last division may also be included pathological chemistry and physics, which treat respectively of the chemical and physical deviations from the normal that occur in disease. Pathology, again, may be general or special, the former dealing with morbid changes and processes irrespective of any individual part, the latter with such changes or processes in individual diseases, tissues, or organs. At the outset the meaning of the term "disease" confronts us. Health and disease are two opposite conditions which shade imperceptibly into each other, and it is often impossible to say where the one ends and the other begins. Health may be defined as that state of the organism in which both structure and function are in the condition which experience has taught us to regard as normal. Disease is, therefore, some deviation of function or of structure from the normal. But since no two individuals exactly resemble each other, difficulty arises as to what should be regarded as the normal. Broadly speaking, however, we have some conception of what is meant by the normal, and the above, or a somewhat similar, definition of disease is the best that can at present be given.

The organism, man or animal, consists of living units or cells, and of non-living or formed material derived from, or laid down by the vital activities of, cells, and frequently dependent on contiguity to and association with the latter for its integrity. Thus, owing to the death and disintegration of cells and alteration in its physical surroundings, the plasma of the blood on being withdrawn from the body undergoes changes which result in the formation of a clot of fibrin and the separation of a fluid serum. Portions of the body largely made up of one kind of cell or formed material are termed "tissues," *e. g.* epithelium, bone, muscle, and tissues are combined in various ways to form organs.

The organism is originally derived from two cells, the male spermatozoon and the female ovum, which fuse to form a single cell, the fertilised egg-cell. This under favourable conditions undergoes division, first into two, then into four, eight, sixteen, and ultimately into an enormous number of, cells, forming the embryo. The organism is, therefore, influenced by the sum of the forces primarily derived from the parents, and is subject to the phenomena which are comprised under the term "heredity," which are active, not only *in utero,* but also after birth.

Influences from without—that is, environment—also materially affect the organism. Inherited and acquired morbid conditions may therefore be distinguished. Diseases would be best classified as *inherited,* derived directly from the reproductive cells before conjugation, *congenital,* arising during intra-uterine development, and *post-natal,* acquired after birth. The terms "inherited" and "hereditary" are somewhat loosely used. They mean, strictly, that the morbid condition is transmitted from the parent to the child, as is the case in congenital syphilis and rarely in tuberculosis. Frequently they are used to denote a morbid predisposition which renders the organism abnormally susceptible, as is the case with gout and generally with tuberculosis. Should development *in utero* proceed abnormally and the form or structure of a part deviate from the normal, an hereditary or congenital malformation results. Such malformation may not in any way interfere with the functions of the organism, but should it do so the condition is known as a congenital disease. It is to be noted that there is little or no evidence that an *acquired* defect or mutilation can be transmitted to the offspring.

If for any reason during development a cell group is not formed which normally ought to be, the structure which should result will be partially or entirely deficient in the mature organism; if partially lacking, the condition is known as hypoplasia, if completely so, as aplasia. As the opposite of this, there may be over-growth, excessive cell proliferation; this is hyperplasia. A third change sometimes met with is a transformation of one fully-formed tissue into another; this is termed metaplasia; *e. g.* cartilage may become fatty or change into bone, fibrous tissue into mucoid tissue, etc. It is to be noted that tissues of one embryonic layer do not change into those of another—*e. g.* fibrous tissue into epithelium, or *vice versâ*.

If parts already formed undergo degeneration or destruction, the process is known as retrogression. Retrogressive changes may be followed by repair more or less complete; this is regeneration. The cells of the body, after living for a longer or shorter period, lose their vitality and die. Permanent cessation of all the functions of the cell constitutes the death of the cell and is not necessarily at first correlated with obvious change in structure. The duration of the vitality of cells is not known with certainty, but it is believed that the cells of higher development, *e. g.* epithelium and nerve, are shorter lived than those of fibrous tissue for example, and that during the life of the organism the cells of the body are replaced by young cells, as the old ones die, many times. The permanent cessation of the functions of the organism as a whole constitutes its death—somatic death as it may be termed, to distinguish it from cellular death. But though the functions of the organism as a whole have ceased, the cells and tissues constituting the organism which has died for some time retain their vitality, and the difference between somatic death and the death of the individual cells and tissues which goes on during life is, in the words of

Foster,[1] that while "the living body, like the dead, is continually losing energy, unlike the dead body, it is, by means of food continually restoring its substance and replenishing its store of energy. The characteristic of the dead body is that, being a mass of substances of considerable potential energy, it is always more or less slowly losing energy, never gaining energy; the capital of energy present at the moment of death is more or less slowly diminished, is never increased or replaced."

The death of the individual cells and tissues which is continuously going on during the life of the organism is more a physiological than a pathological process, and is a senile change or retrogression.

The cell nowadays is regarded as having a complex structure. A cell is described as consisting of cell protoplasm or cytoplasm, containing a nucleus and an attraction sphere, and often one or more vacuoles and various granules. The cytoplasm is regarded as having a foam-like structure, and to consist of a relatively fluid substance, or hyaloplasm, contained within the meshes of a sponge of a more solid material—the spongioplasm. The nucleus is regarded as being delimited by a membrane and to consist of a matrix of a substance (linin) which stains with difficulty, imbedded in which are a number of granules having a strong affinity for certain dyes, and termed "chromatin," which chemically belongs to the nucleins. The nucleus contains one or more bodies termed "nucleoli," some of which are mere aggregates of chromatin (karyosomes); others may be specialised bodies (plasmosomes). The attraction sphere is a small body lying near the nucleus and containing two granules—the centrosomes; it seems to be of importance in cell division.

Cell division is always preceded by division of the nucleus. This may take place either in a simple manner, or as a result of a complicated re-arrangement and fission of the nuclear constituents. The former is termed "direct or amitotic division," the latter "indirect or mitotic division," and the process "mitosis or karyokinesis." Amitosis is infrequent in the higher animals; it occurs in nutritive gland cells, in the follicular epithelium of the ovary, and in the "foot" cells of the testis.

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[1] *Text-Book of Physiology*, ed. 5, p. 2.

THE CAUSES OF DISEASE.

The causes of disease are manifold, and omitting from consideration those which are due to imperfect structure as a result of abnormal development, can usually be traced to external causes. Some pathologists assert that *all* disease processes are the result of external causes, acting, if not on the individual, on the ancestors of the individual—a proposition difficult to prove or disprove.

As already mentioned (p. 3) imperfect or abnormal development *in utero* may give rise to a condition incompatible with normal life, and a congenital disease ensues—*e. g.* stenosis of the aorta or deformity of the cardiac valves.

If the closure of the *foramen ovale* between the two auricles of the heart does not take place soon after birth, as it normally should, a diseased condition ensues, usually termed "a form of congenital heart disease," but hardly strictly so, since it arises after birth. Many forms of imperfect development are quite compatible with normal life, and are then spoken of as malformations—*e. g.* club-foot, malposition of organs, hare-lip, extroversion of the bladder, etc. It is to be noted that it is not the abnormality of structure, the malformation, that is the disease, but the disturbance of function which results therefrom. Leaving out, then, those diseased conditions which are due to defects of structure, the congenital and allied diseases, the causes of disease are usually divided into (1) predisposing, and (2) immediate, exciting, or determining. Among predisposing causes may be mentioned heredity, which leads to some inherent weakness, rendering the organism more vulnerable, as is frequently the case with tuberculosis and gout. Climatic conditions, youth and old age, heat and cold, and other conditions, may have a similar action. Thus, in the case of pneumonia cold or chill seems to lower the vitality and render the tissues vulnerable to the attack of the pneumococcus; many infective diseases, such as diphtheria and scarlatina, are much more common in young individuals than in adults; while rats, which are naturally insusceptible to anthrax, may be rendered so by fatigue. The immediate or exciting causes of disease may be classified as follows:

(1) *Traumatism.*—Wounds, blows, crushes, pressure, and all mechanical injuries are fertile causes of disorder of structure or of function.

(2) *Thermal effects.*—A temperature above or below a certain point induces an abnormal condition, and if long continued or excessive in either direction, may lead to death—local or somatic. It is to be noted that both heat and cold are included under thermal causes, and are familiar as burns and frost-bite. Heat and cold, without producing gross lesions such as these, also induce peculiar abnormal conditions, which will be discussed under the subject of Pyrexia.

(3) *Electricity* may cause an abnormal condition or death, and acts partly thermally, burning the tissues, as is frequently seen in lightning-stroke, partly by a peculiar action on the nerve centres, inducing inhibition, and partly, perhaps, by electrolysis of the tissues and of their constituent organic compounds.

(4) *Peculiar radiations,* such as the X and radium rays, also induce abnormal conditions in living organisms.

(5) *Variations in atmospheric pressure.*—Exposure to extreme atmospheric pressure, as in divers, those employed in air-locks in bridge or tunnel-making (caisson disease) and exposure to diminished pressure as at high

altitudes, in balloons, etc., induce disturbances of the normal physiological balance.

(6) *Chemical agents,* such as strong acids and alkalies, arsenic, etc., produce locally gross changes where they come in contact with the tissues. This action must be distinguished from that which obtains with the members of the next group.

(7) *The chemical poisons.* The alkaloids, such as morphine and strychnine, hydrocyanic acid, and a host of substances have a peculiar action in inducing abnormal conditions, when introduced into the living organism in relatively small quantities. They differ from the members of the preceding group in that no matter where or how each is introduced it gives rise to its own peculiar effect—*e. g.* the tetanic convulsions produced by strychnine, the paralysis of the respiratory and cardiac centres produced by hydrocyanic acid, morphine, and aconite, and so on. Susceptibility to poisons varies considerably with age, mode of administration, acquired tolerance, and the like. Thus, children are relatively more tolerant to mercury and belladonna than adults, adults to opium than children; dogs bear intravenous injections of atropine well, but are readily poisoned by intra-spinous injection. By taking arsenic or opium in gradually increasing doses a marked tolerance for the drug is acquired.[1] The poisons do not seem to enter into a strict chemical combination with the tissues, as is the case with the toxins of microbial diseases belonging to the next group, but are regarded as being in a state of "solid solution" analogous to that of the constituent metals in an alloy; for strychnine and morphine, for example, can be extracted from the tissues by simple

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[1] This acquired tolerance is known as "Mithridatism," after Mithridates the Great, King of Pontus, who is said to have fortified his constitution against poison by a course of treatment.

solvents, such as ether and amylic alcohol, which would hardly be the case if there were a chemical combination. Some of the inorganic poisons, as arsenic, may be taken up by the leucocytes. After absorption, poisons are got rid of in various ways, by excretion from glands—*e.g.* the salivary glands in mercurial poisoning—by destruction in the blood, tissues, and organs, especially the liver. Recent researches have shown that arsenic in minute quantities is a natural constituent of the body, and is being continuously eliminated by the hair, nails, and menstrual blood.

(8) *Microbial infections* form a large and important class of diseases.

They are due to the growth and multiplication of vegetable organisms, minute and unicellular, the bacteria and yeasts, or larger and multicellular, such as fungi, in the tissues. Many of the specific fevers, infectious and contagious disorders belong to this group. They may usually be propagated by direct inoculation, and are frequently contagious or infectious or both. The terms "contagious" and "infectious" denote, the former that close contact is generally necessary in order to produce infection, as in syphilis and diphtheria, the latter that the infection may readily be carried for a distance from the sick person, as is the case with smallpox and scarlatina. The distinction between contagious and infectious is relative and one merges into the other. Moreover, there are diseases belonging to this class, and certainly due to microbial infection, such as tetanus and leprosy, which are but slightly and not obviously contagious, much less infectious, and to include all these gradations and avoid ambiguity it is preferable to abandon the terms "infectious" and "contagious" and to speak of them as *infective*.

Should poisoning ensue from chemical poisons elaborated by micro-organisms and absorbed as such, ptomaines, toxalbumins, etc., it would be included in this group, but is preferably termed an intoxication. This sometimes occurs with tinned foods, sausages, etc., and is known as "ptomaine poisoning."

(9) *Parasitic infections* form another important class of diseases due to infection with animal parasites, unicellular protozoa as in malaria, or multicellular metazoa such as the tape and other worms, flukes, etc. The microbes of microbial infections are just as much "parasites" as those of parasitic infections, but it is customary and in many ways convenient to retain this distinction. Moreover, in the majority of parasitic infections the infecting agent is conveyed, not directly, but through some intermediate host which harbours the parasite, and in which a developmental cycle is usually passed.

These two classes of microbial and parasitic diseases will be further considered in a subsequent chapter.

(10) *Auto-intoxication* as a cause of disease has only comparatively recently been recognised and is still obscure. It denotes an intoxication due to the products of abnormal metabolism, or arising from diminished or excessive or disordered secretion or excretion in the organism. The poison is, therefore, a product of the organism's own organs, tissues, or cells. The products of digestion when injected are found to be toxic, and the symptoms, such as headache, lassitude, somnolence, etc., so frequently seen in disorders of the liver and digestive tract are probably due to the absorption of substances which have not undergone the normal changes in the intestinal mucosa and liver, and therefore act as poisons. When bile is retained disordered cardiac action, itching of the skin, etc., frequently occur. Uræmia is another instance of auto-intoxica-

tion. In athletes and others, the subjects of prolonged muscular exertion, especially if for any reason elimination by the skin and kidneys is diminished, serious symptoms, such as coma and convulsions, are occasionally seen and are regarded as being due to auto-intoxication, the result of the accumulation of waste products. Muscular fatigue is similar in nature and largely due to the accumulation of waste products; if these be rapidly removed, the occurrence of fatigue is much retarded. The disorders following abnormal conditions of the thyroid and adrenals have also been attributed to auto-intoxication, but these will be considered later.

Auto-intoxication is classified by Vaughan and Novy[1] as follows:

(1) The digestive organs may perform their functions imperfectly, and the products of their incomplete action may be absorbed and lead to disturbance in certain organs.

(2) Certain secretions and excretions may be poisonous when brought into contact with tissues with which normally they have no relation. Thus, bile-acids have a hæmolytic action when absorbed into the circulation.

(3) It seems to be the function of certain organs to prevent the passage of certain substances into the general circulation, *e.g.* the thyroid gland.

(4) The retention of excrementitious substances leads to disturbance of health, *e.g.* urates in gout and bile in jaundice, while leucomaines are continually being produced, and if retained within the body result in disturbance.

(5) Certain cells may fail to adjust themselves to general alterations taking place elsewhere—*e.g.* the disturbance that accompanies the periods of puberty and of the climacteric.

(6) Under conditions not fully understood, certain cells may fail to utilise certain food-stuffs, with resulting intoxication, *e.g.* carbohydrates in some forms of diabetes.

(7) Active poisons, leucomaines, cholin, acids, gases, etc., may sometimes be generated by certain cells.

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[1] *Cellular Toxins*, 1903.

CHAPTER II.

THE PROGRESSIVE AND RETROGRESSIVE CHANGES.

THE PROGRESSIVE CHANGES.

Hypertrophy, Hyperplasia, and Regeneration.

The elements of the tissues are continually wearing out, as it were, and new cells are produced to take the place of the old ones. The various tissues are also regenerated after loss of substance by the ordinary wear and tear of life, or by traumatism or necrosis, and the changes which result in the proliferation of cells and regeneration of tissues are termed "progressive."

The progressive changes consist essentially in the formation of new cells, and in some cases in the enlargement of existing ones, the original tissue being reproduced, or replaced by a simpler tissue. If the formation of new tissue does not go beyond that required to replace the old, the process is *regeneration*; if the new tissue be in excess of this, the process is *hypertrophy* or *hyperplasia*.

SIMPLE HYPERTROPHY is an enlargement due to an increase in size of the tissue elements, as in a muscle which may become enlarged simply from an increase in size of the muscle-fibres.

NUMERICAL HYPERTROPHY OR HYPERPLASIA is an enlargement due to multiplication of the tissue elements. Hypertrophy and hyperplasia generally go together, as in the cardiac muscle in certain forms of enlargement of the heart, and in the pregnant uterus, in which the muscle-cells become much more numerous; and the term "hypertrophy" is often used to include both simple hypertrophy and hyperplasia.

If the tissue of a hollow organ (*e. g.* the heart or bladder) undergoes increase, the cavity enclosed is lessened in size; this is known as *concentric hypertrophy.* When part of an organ or tissue is lost, the remainder frequently undergoes a *compensatory hypertrophy,* and this occurs in the heart and bladder if a resistance above the normal has to be overcome, as when the vessels are diseased or there is stricture of the urethra. If one kidney is destroyed, its fellow undergoes enlargement, and considerable loss of liver or spleen substance may be followed by increase in the remainder.

Increase in physiological activity within limits is always followed by hypertrophy. In some instances the cause of hypertrophy is obscure, but is probably dependent on chemical changes and the influence of internal secretions, as an example of which the enlargement of certain bones in acromegaly may be quoted.

Regeneration.

Regeneration is the process whereby tissue which has been lost is replaced by new tissue of the same, or approximately the same, kind as the original. In man the power of regeneration is limited, and the higher the tissue, the smaller the tendency to regeneration. Thus it is doubtful if ganglion cells are ever reproduced, the regeneration of glandular cells and striated muscle is limited, while surface and duct epithelium, and particularly connective tissues, have a considerable capacity for regeneration.

To a large extent the regenerated tissue arises from tissue of the same kind. Thus epithelium develops only from epithelium and muscle from muscle. Even one type of epithelium can frequently be derived only from epithelium of the same kind, *e. g.* glandular epithelium.

Regeneration is necessarily often imperfect, and connective tissue takes the place of the special tissue; this is scar-formation. Why the proliferation of cells should have a limit cannot be completely explained; it probably depends on mutual pressure between the constituents of the tissue, on chemical conditions connected with its nutrition, and on other factors of which we are ignorant.

FORMATION OF NEW BLOOD-VESSELS. — New blood-vessels are necessarily formed whenever any degree of regeneration or hyperplasia takes place. They develop as offshoots from the walls of existing capillary vessels. An endothelial cell becomes swollen and sends out a wedge-shaped outgrowth, ending in a fine protoplasmic thread; this may meet with another similar endothelial prolongation, or with another capillary, or may bend back to the vessel from which it originated. Nuclei appear in the granular protoplasm of the outgrowth which then gradually becomes hollow or canalised, the blood enters it, the excavation proceeds, and ultimately extends to another capillary, and thus a new capillary is formed. At first the wall of the new capillary is homogeneous, but subsequently the protoplasm collects around the nuclei, which in the meantime have been dividing, and thus the new endothelial cells become differentiated. If arteries and veins are eventually developed, they originate by a dilatation of newly-formed capillaries with a corresponding thickening of their walls, but the manner in which the latter phenomenon is brought about is not clear.

The *regeneration of leucocytes* takes place in the lymph glands and follicles, in the spleen and lymphoid bone-marrow, also by division of pre-existing leucocytes.

The *regeneration of chromocytes* is believed to take place in the red bone-marrow from nucleated red cells, the hæmatoblasts, the nuclei of which disappear, and so the non-nucleated chromocytes are produced. If regeneration be very active, as after severe hæmorrhage, nucleated red cells frequently appear in the peripheral circulation.

REGENERATION OF EPITHELIUM takes place from epithelium. The epithelium around the site of injury proliferates and spreads over the denuded surface. In the skin, the epithelium of the sweat and sebaceous glands may take part in the regeneration. Hair and nail are reproduced provided portions of the hair-follicles or of the nail matrix remain undestroyed. Glandular epithelium is also rapidly reproduced, particularly in the liver, also in the renal tubules, gastric mucous membrane, etc.

As a general rule each kind of epithelium produces its like, but this is not universal. Thus, in inversion of the uterus, the cubical epithelium may become converted into squamous.

REGENERATION OF MUSCULAR TISSUE is usually limited, the new muscle being derived from neighbouring muscle, not from connective tissue. The regeneration commences by the division of the nuclei of the muscle-fibres or cells.

REGENERATION OF CONNECTIVE TISSUES.—This is generally very free. New *fibrous tissue* commences by proliferation of the fixed connective-tissue cells known as fibroblasts, or, possibly, from certain leucocytes or other wandering cells. In the earlier stages the fibroblasts are rounded, and afterwards become spindle-shaped; they seem to lay down, as it were, structureless fibrillæ, which subsequently become the connective-tissue fibres. New *cartilage* is derived from cells, chondroblasts, mostly derived from the periosteum or perichondrium. *Bone* arises from cells, osteoblasts, of the periosteum or perichondrium. The osteoblasts become separated by a homogeneous or fibrillated ground substance in which lime-salts become deposited, the osteoblasts becoming the bone-corpuscles of the lacunæ of the mature bone. Cartilage and fibrous tissue may also change into bone. *Adipose tissue* may be formed by a deposition of fat in various connective-tissue cells. *Mucous tissue* usually arises by metaplasia (see below).

REGENERATION OF NERVE-TISSUE.—It is doubtful if ganglion cells can be reproduced, at least in the adult. Nerve-fibres of the peripheral nerves are capable of considerable regeneration, but not those of the central nervous system.

METAPLASIA is the name given to the transformation of one kind of tissue into another. Thus cartilage and fibrous tissue may be converted into bone, fibrous tissue into myxomatous tissue, etc. In the latter, the fibrillated intercellular substance disappears and its place is taken by mucoid material, and at the same time the connective-tissue cells change into cells with interlacing processes. Myxomatous change occurs in myxœdema.

THE RETROGRESSIVE CHANGES.

Atrophy.

ATROPHY is the decrease in size and number of the constituent elements of a tissue. It is a retrogressive change affecting parts already well formed and properly developed, and must be clearly distinguished from defective development, which is hypoplasia.

Atrophy may occur physiologically in the thymus early in life, in the uterus after parturition, and in the female genital organs after the menopause. Such physiological atrophy is better termed "involution."

SIMPLE ATROPHY.—Towards the close of life, organs and tissues frequently undergo retrogressive changes analogous to the physiological atrophy or involution mentioned above. This is well seen in old people, in the skin, which becomes thin and wrinkled. Occasionally similar changes occur prematurely; these are not preceded by any obvious degenerative changes; the cells of the part undergo gradual diminution in size and ultimately lose their nuclei and become disintegrated and absorbed, an increase in pigmentation frequently accompanying the atrophic process. This is termed "simple atrophy," and may occur in the ganglion cells of the central nervous system, in glandular organs, such as the liver and kidney, in the muscles, lungs, and in bone. It is always the specific tissue elements, such as the glandular cells, muscle-fibres, etc., which atrophy, and not the supporting connective tissue, and the organ or tissue generally diminishes in size.

A certain degree of physiological activity is necessary to maintain the integrity of a tissue, and a gland or muscle condemned to inactivity for any length of time atrophies. Thus, the muscles of a broken limb kept at rest in splints or of a paralysed limb atrophy. This is known as the *atrophy of inaction.*

Tissues exposed to prolonged pressure atrophy, *e. g.* bone pressed on by an aneurysm—*pressure atrophy.* The central nervous system exercises an important function as regards the nutrition of the tissues, the best example of which is the rapid atrophy of muscles that ensues when their trophic centres (the ganglion cells in the anterior horns) are damaged. This has been termed *trophoneurotic atrophy.*

Atrophy also occurs from defects of nutrition, as in starvation, general or local, in wasting diseases, *e. g.* tuberculosis and malignant disease, and in disease of the vessels.

Necrosis.

By necrosis is meant the death of individual cells, groups of cells, or portions of tissues while still constituents of the living body. Necrosis which is preceded by retrogressive changes in the cells is sometimes termed *necrobiosis.* Necrosis is caused by the various agencies which bring about disease generally, viz. traumatic, mechanical, chemical, thermal, electrical, and toxic, and also by arrest of nutrition, usually through interference with the blood supply. Frequently two or more of these factors act concurrently. In necrosis of the cell the nucleus becomes indistinct and stains indifferently or hardly at all, the chromatin undergoes a kind of solution or *chromatolysis*, or sometimes breaks up into small irregular fragments, *karyorrhexis,* while the cytoplasm loses its granulation and becomes glassy or *hyaline,* and occasionally vacuolated. In some instances a coagulative exudation saturates the necrotic area, giving rise to *coagulative necrosis.*

The various forms of necrosis may now be considered.

FOCAL NECROSIS.—Small areas of tissues or organs often undergo necrosis in the course of infective diseases, particularly in typhoid and diphtheria, after burns, and after poisoning with animal and vegetable toxalbumins; these are known as "focal" or "insular" necroses. They are most frequently seen in the liver, spleen, and lymph-glands. In the majority of cases the nucleus of the cells undergoes karyorrhexis, occasionally chromatolysis, the cytoplasm becomes hyaline, the outlines of the cells become indistinct and finally lost, and a granular detritus takes the place of the original tissue. When the process comes to an end, leucocytes may collect at the periphery, some of which may die and nuclear detritus accumulate, but finally the whole may be absorbed, or newly-formed connective tissue replace the necrotic. The exact causation of focal necrosis probably depends on toxic substances which may act directly on the cells and capillary endothelium of the area and cause their death, or may induce capillary thrombosis and anæmic necrosis.

FAT NECROSIS.—This is a remarkable condition especially affecting the fat of the abdomen, omentum, etc., and met with in connexion with inflammatory diseases of the pancreas. It appears in the adipose tissue as whitish opaque areas of variable but appreciable size in which the fat cells are found to be converted into a granular detritus which remains unstained with osmic acid. The condition is regarded as being caused by the escape of a fat-splitting ferment or lipase (steapsin) from the pancreas. Fat necrosis has been produced experimentally by injecting pancreatic extract and by ligation of the vessels at the splenic end of the pancreas. Flexner[1] has isolated a lipase from the necrotic areas.

COAGULATIVE NECROSIS is characterised by the saturation of the necrotic tissue with an exudation which coagulates with the formation of fibrin or of a fibrin-like substance. In some instances this coagulative exudation escapes from the vessels, in others the cells and cellular structures probably supply it, at least in part, and the whole coalesces into a hyaline mass. The former frequently occurs in inflammatory conditions, and the exudation may be poured out on to a surface and coagulate there, forming a *false membrane*. In the latter, which results from the action of chemical and thermal agents or by arrest of nutrition, the cells die, the part is bathed in lymph, and a general coagulation ensues, the cellular and tissue elements lose their outlines and become a hyaline mass, but the process of dying must not be too protracted, or fatty or other degenerative changes may intervene and render the cells non-coagulable. In diphtheria a combination of the two processes occurs to form the false membrane: a coagulative exudation is poured out on to the surface of the mucous membrane, and the elements in the superficial layers of the membrane undergo a coagulative necrosis.

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[1] *Journ. Exper. Med.*, vol. ii, 1897.

In striated muscle a necrosis known as Zenker's, or waxy degeneration, occurs and is regarded as a coagulative necrosis of the muscle-fibres. The muscle-plasma coagulates and breaks up into shining lumps and the fibres loose their striation. It is met with in febrile diseases, such as typhoid, and chiefly affects the muscles of the abdominal wall. The affected muscles become pale, semi-opaque, and lustreless, and are described as looking like fish muscle.

In the anæmic infarct (see Chapter XII, p. 264) coagulative necrosis takes place.

COLLIQUATIVE NECROSIS is a form of necrosis attended with softening and liquefaction of the necrotic area. It seems to occur in tissues saturated with liquid which has little tendency to coagulate. The cells become enormously swollen and distended with fluid, soften, and disintegrate, the process being a kind of solution, due in all probability to ferment action. Through the work of Hedin and others it has been found that the organs, tissues, and fluids of the body contain proteolytic ferments, and these may be the active agents in colliquative necrosis. It is met with in the brain and cord as a result of thrombosis or embolism, in which the anæmic necrosis thereby produced undergoes this process of softening.

Caseation must be regarded as a post-necrotic change in which the necrosed area becomes converted into a structureless cheesy mass of varying consistence, composed of fatty and albuminous granular detritus. It is typically met with in tuberculous lesions, particularly in the lymph-glands, and also occurs in syphilis, in inflammatory lesions, and occasionally in rapidly growing tumours. Caseous matter may be absorbed, or become encapsuled or calcified.

Gangrene is a term applied to necrosis of large portions of an organ, tissue, or member. Two forms are met with, the dry and the moist.

Dry gangrene occurs in parts, particularly the extremities, freely exposed to the air, such as the foot, hand, nose, ear, etc. It is typically seen in senile gangrene of the extremities and in frost-bite. The tissues become livid and discoloured, due to the blood-colouring matter in the part escaping from the vessels. Evaporation from the surface goes on at the same time and the tissues begin to shrink and wither, the epidermis tends to peel, and this still further hastens the drying process. Ultimately, the part affected becomes black, dry, withered, and brittle. At the junction of the dead and living tissues a zone of inflammatory reaction is conspicuous as a dusky red band, which is known as the *line of demarcation*. Dry gangrene is usually dependent on disease of the blood-vessels (atheroma and arteriosclerosis), which diminishes their calibre and renders them tortuous and rigid, and so interposes an obstruction to the blood-flow, which favours thrombosis and embolism. Feeble heart's action frequently adds to the difficulty of maintaining the circulation. Dry gangrene is therefore a form of anæmic necrosis; it occurs physiologically in the stump of the umbilical cord in the infant.

Moist gangrene occurs when the necrotic tissues become invaded with bacteria and undergo putrefactive decomposition, which usually happens when the part is infiltrated with blood and exudation. The tissues become green and black, softened and stinking, and total disintegration may finally ensue. Toxic substances may be absorbed and lead to a sapræmia. Moist gangrene may attack the extremities, also the lungs, bowel, uterus, etc. The causes bringing it about are generally traumatism, burns, etc., local pressure in a debilitated subject, *e. g.* bed-sores in typhoid, and cardiac insufficiency, with œdema and dropsy.

Emphysematous gangrene is a form of moist gangrene accompanied with tho production of a considerable amount of gas in the tissues, giving these a crepitant feeling to the touch, with bullæ under the epidermis. It occurs particularly with lacerated, contused, dirty wounds and is due to infection of the tissues with the *B. aërogenes capsulatus* of Welch (and possibly other similar organisms). The process spreads rapidly, there is considerable exudation, and general intoxication is frequent.

Other causes of gangrene are nerve-lesions, as in Raynaud's disease, in which extreme spasmodic contraction of the arterioles is regarded as inducing anæmic necrosis, trophic disturbance as in spinal disease, such as acute myelitis, in which the acute decubitus or bed-sore develops, which, though favoured by the fact that the patient, being paralysed, is unable to move, can scarcely be the result of pressure, since it may develop with extreme rapidity. Chronic poisoning with ergot also induces contraction of the arterioles and anæmic necrosis of the extremities, arteriosclerosis usually contributing to the result. The X rays also seem to bring about necrosis if used without proper care or protection, but the mode of production is uncertain.

Should the patient survive long enough, the gangrenous part may become completely separated from the living by infiltration with leucocytes and phagocytic cells in the inflammatory zone at the line of demarcation. Needless to say, this process would take a very long time if the gangrenous mass be large, and particularly in the case of bone, but this too may ultimately be separated from the living.

Surgically, if a small portion of the soft tissues necroses, the process is often termed *sloughing* or *sphacelation* and the necrotic mass a *slough* or *sphacelus*, the term "gangrene" being reserved for the simultaneous loss of vitality of a considerable mass of tissue. If a portion of bone dies, *necrosis* is said to have occurred, and the necrosed mass is a *sequestrum*. *Phagedæna* is a form of spreading sloughing attacking the prepuce, glans penis, or even the body of the penis, and occasionally an inguinal bubo, in venereal disease. In certain tropical countries sloughing phagedæna (non-venereal) of various parts occurs, and is a serious affection. *Wound phagedæna* and *hospital gangrene* in pre-antiseptic days used to attack operation wounds. *Cancrum oris* is a gangrenous stomatitis, and *noma* a gangrenous vulvitis, both attacking young children.

The Degenerations and Infiltrations.

DEGENERATION is a process whereby cells, tissues, or tissue elements are structurally altered so that they can no longer maintain their functional activity, and undergo either disintegration with separation into simpler constituents, or a re-arrangement of their constituents with the formation of new and abnormal products.

Infiltration is a process whereby a substance circulating in the blood, an ordinary constituent or one not usually there, is deposited in an organ or tissue normally free from it, or, if naturally present in the tissue, is deposited in excessive amount.

Practically, it may sometimes be very difficult to distinguish between an infiltration and a degeneration.

Cloudy swelling is a change of very frequent occurrence in the tissues and organs. It affects the epithelial and connective-tissue cells; they become swollen and enlarged and lose their regular outline, the nucleus becomes indefinite and its chromatin stains indifferently, or in advanced cases it disappears (Fig. 1), and the cytoplasm becomes filled with fine granules which are soluble in acetic acid, but insoluble in alkalies and ether. Finally, the cells may break up into a granular detritus

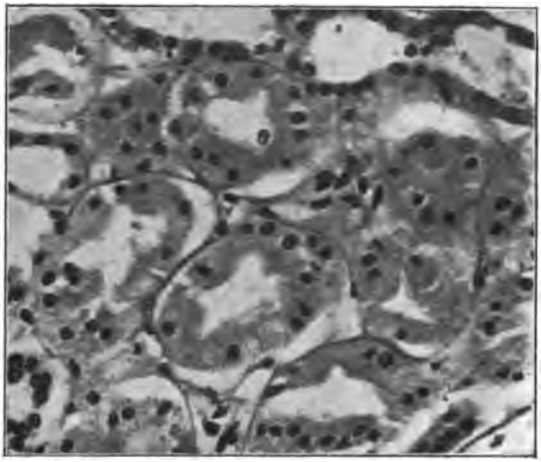

Fig. 1.—Cloudy swelling of renal epithelium (hæmatoxylin and eosin. × 250).

and the process is often associated with fatty degeneration. If not too advanced, the process may cease, regeneration follow, and the cells return to their former normal condition.

Cloudy swelling is a frequent accompaniment of fever and inflammation, and is commonly seen in infective diseases, especially enteric and scarlet fevers, diphtheria, and septicæmia. The process is met with in these conditions in the heart-muscle, liver, and kidneys, and in local inflammations the connective-tissue cells may undergo similar changes. The affected organs and tissues are paler than normal, contain little blood, and have a dull, cloudy, greyish appearance and doughy consistence.

Dropsical swelling is akin to the foregoing, and the cells of the part show much the same changes. It occurs in dropsy and inflammation, the cells becoming infiltrated with fluid and swollen and degenerate. The process, perhaps, is primarily an infiltration with fluid, degenerative changes in the cells then ensuing.

Mucoid degeneration is met with as a physiological process in the epithelium of mucous membranes in the form of goblet cells. Pathologically, it is seen in catarrh of mucous membranes, in which the epithelial cells become affected, and in the connective tissues in myxœdema. The cells and fibres become swollen and transformed into a glassy, jelly-like material which gives the reactions of mucin, viz. it swells up in water, is soluble in dilute alkalies, particularly lime-water, from which it is precipitated by acetic acid and by alcohol. Boiled with dilute acids, it gives rise to a substance reducing cupric oxide. It is stained a reddish purple colour with thionin and toluidin blues.

The cells of pathological new formations frequently undergo mucoid degeneration, *e. g.* cancer, particularly in the abdomen, and sarcoma. In ovarian cysts the process, though similar, results in the formation of pseudomucin, which differs from true mucin in being non-precipitable by acetic acid.

A tumour which is mucoid from the first is known as a myxoma, and is to be distinguished from one in which mucoid degeneration of its elements occurs.[1]

COLLOID DEGENERATION is particularly met with in the thyroid gland, where colloid material is normally present, and also occurs in the cells of the hypophysis cerebri, kidney, adrenals, and prostate. The microscopical characters are much the same as those of mucoid degeneration, but the colloid substance is not precipitated by acetic acid nor by alcohol, in these respects resembling pseudomucin. The so-called colloid cancer (*e. g.* of the omentum) is probably really a mucoid degeneration.[2]

Colloid is stained orange-red by van Gieson's stain (Delafield's hæmatoxylin and picric acid and fuchsin).

HYALINE DEGENERATION attacks especially the connective tissues, which it renders glassy and homogeneous. It superficially resembles the lardaceous substance both in appearance and situation (but may occur in cells), but does not give the lardaceous reactions, nor has it any particular relation with chronic suppuration. Hyaline degeneration occurs chiefly in the adventitia of the smaller arteries, particularly in the lymphatic glands, brain, and kidney, appearing as glassy homogeneous masses outside the endothelium. The hyaline material stains yellow with iodine, and red with van Gieson's stain, and (like lardacein) pink with methyl violet, but the colour is very unstable and is quickly discharged by 1 per cent. hydrochloric acid. Many observers have suggested that hyaline degeneration is a precursor of lardaceous infiltration, and Green's experiments on lardaceous disease give additional confirmation of this view (see next section).

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[1] The ordinary mucous polypus of the nose is strictly an œdematous fibroma. True myxomata are of rare occurrence.

[2] There are probably several varieties of the colloid material which have not yet been exactly differentiated. The normal colloid of the thyroid contains iodine.

Lardaceous infiltration.—Amyloid, waxy, or lardaceous degeneration, or rather infiltration, is a condition affecting the connective tissues and leading to the deposit of a special protein body, the amyloid or lardaceous substance. Organs the seat of advanced lardaceous infiltration are enlarged, often much so, the margins, if thin, become thickened and rounded, the consistency is greatly increased, and the cut surface has a mottled greyish appearance, and thin sections are more or less translucent. It is most frequently seen in the spleen, liver, kidneys, stomach, intestines, and lymphatic glands, but may occur in other parts, *e. g.* the heart, aorta, and muscles, the pancreas, adrenals, and thyroid. The change often appears in scattered patches, which look like boiled sago or tapioca, hence the name "sago-spleen." The lardaceous substance gives characteristic reactions. If the blood be first washed off a cut surface of the organ, which is then flooded with iodine solution[1] and again washed, the lardaceous material will be found stained a deep mahogany brown, while the surrounding tissues are of a pale yellow colour. Microscopical sections of the fresh tissue may be similarly treated. Hardened tissues also give this reaction, but not so well as fresh ones. Iodine and sulphuric acid (5 per cent.) sometimes give a blue colour (*cf.* cellulose), but this reaction is uncertain. It was from this that Virchow gave the name "amyloid," as he regarded the material as being carbohydrate in nature and allied to cellulose. The reaction is greatly dependent on the physical condition of the lardaceous material (Hammarsten); by some it has been supposed to be due to admixture with cholesterin. With methyl violet, or gentian violet, the lardaceous material (fresh or hardened) gives a deep rose-pink, which is very stable (contrast with hyaline degeneration); after staining in an aqueous solution of the dye, the sections should be rinsed in water acidulated with acetic acid, and mounted in glycerin; methyl and iodine greens also give a pink colour.

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[1] Iodine, 1 part; potassium iodide, 10 parts; distilled water, 100 parts. It is often a good plan before applying the iodine to rinse the surface with dilute acetic acid (20 per cent.).

The lardaceous or amyloid substance (lardacein) is a protein body decomposed by alkalies into proteid and chondroitin-sulphuric acid. It is white and amorphous, and insoluble in alcohol, ether, and dilute acids and alkalies. Concentrated acids and caustic alkalies dissolve it with decomposition. On boiling with dilute hydrochloric acid, it yields sulphuric acid and a reducing substance. It is generally stated to be undissolved by gastric digestion, but by this treatment becomes soluble in dilute ammonia.

The lardaceous substance is primarily formed or deposited in the connective tissues of the arteries, particularly the smaller ones. If microscopical sections of the tissues in the earlier stages be studied, it will be found that the lardacein is deposited in the periendothelial connective tissue, and the endothelium appears coated with a glassy layer, here and there broken up into lumps. In the kidney the process commences in the glomerular tufts and in the intertubular arteries (Fig. 2), in the liver between the capillary endothelium and the liver-cells; in the spleen the walls of the smaller vessels are usually involved, but it is often confined to the Malpighian bodies, which become enlarged and grey, like grains of sago. The fibrous trabeculæ also suffer in the spleen and lymph-glands, the tunica propria in glands, and the perimysium internum and sarcolemma in muscle. The deposit of the lardaceous substance results in interference with the circulation and pressure on surrounding parts, so that the epithelial cells of the kidney and liver become degenerate and often fatty, and if the process is extensive large areas of organs and tissues may be destroyed, the place of the normal structures being taken by masses of lardaceous material.

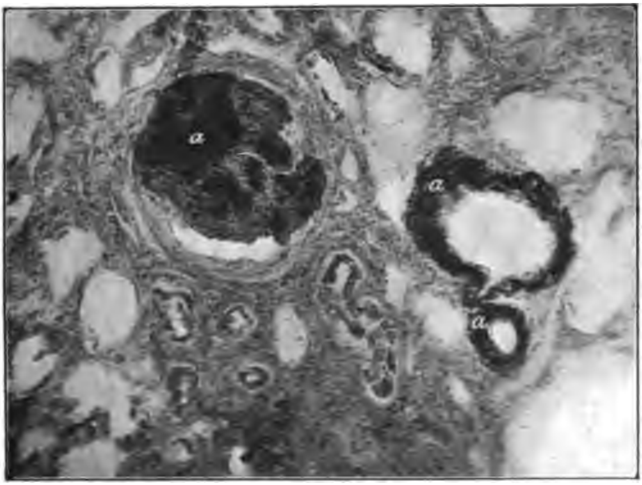

Fig. 2.—Section of lardaceous kidney stained with methyl violet (× 75). *a, a, a,* deposits of lardaceous material in a glomerulus and two small vessels (stained *pink* in section).

Lardaceous infiltration is associated with chronic suppuration, syphilis, and chronic dysentery, and it may develop in as short a time as two or three months (this is unusual), but its histogenesis is uncertain. It does not seem to be a degeneration, as lardacein does not appear in the parenchyma cells. On the other hand, the great insolubility of lardacein seems to preclude the idea that it circulates in the blood and is deposited therefrom, though the constancy with which it appears in the vessel-walls suggests that the deposit is intimately associated with the blood. Czerny has suggested that the substance is formed at the suppurative focus and is carried thence by the leucocytes. Krakow seems to have succeeded in producing lardaceous infiltration in rabbits and chicken by repeated injections of cultures of the *Micrococcus pyogenes aureus.* Green,[1] however, as the result of prolonged injection of the same organism, was unable to induce lardaceous infiltration in rabbits, only hyaline degeneration, but in fowls typical lardaceous disease was obtained after the injections, although suppuration did not occur. Green found that hyaline degeneration always seemed to precede the lardaceous infiltration, and concludes that the hyaline change is a precursor of the lardaceous infiltration. In the blood of hens injected with the *M. pyogenes aureus* there was always a marked increase in certain eosinophile cells, and Green suggests that these cells may be intimately associated with the lardaceous deposit, the granules being deposited in the walls of the vessels, and being the precursors of the lardaceous substance.

Corpora amylacea.—In addition to general lardaceous disease, a local lardaceous infiltration may sometimes occur, for example, in granulation tissue and in syphilitic cicatrices. Free amyloid concretions, "corpora amylacea," are also met with, *e. g.* in the prostate and ependyma of the cerebral ventricles. Halliburton states, however, that the corpora amylacea in the brain contain no nitrogen; if so, they cannot be lardaceous. In nerve-tissues kept long in spirit a material like lardacein may be formed—artificial amyloid[1]).

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[1] *Journ. Pathol. and Bacteriol.*, vol. vii, 1901, p. 184.

GLYCOGENIC INFILTRATION.—Glycogen, normally present in considerable, though variable, amount in the liver-cells and in developing embryonic tissues, and in small amount in most cells and tissues, becomes much increased in certain pathological processes. Thus, it is found abundantly in most tumours, and in suppuration is present in the leucocytes (also in pus). In diabetes mellitus glycogen is found in abnormal amount in the leucocytes, and often in the kidney and liver, and in experimental diabetes after extirpation of the pancreas a similar glycogenic infiltration takes place. The test for glycogen is the mahogany colour which it gives with iodine, best applied as a solution in gum-arabic, but the tissues must be removed and fixed in alcohol immediately after death, or post-mortem changes quickly convert the glycogen into sugar.

FATTY INFILTRATION.—Fat occurs normally in various tissues and organs, as stored material, the quantity varying with the amount produced during nutrition and the amount consumed in the katabolic processes of the body. If the amount produced be in excess or the amount consumed be diminished, the storage fat increases, and if this increase passes certain limits it becomes abnormal, and the condition known as obesity or lipomatosis results. The process leading to this condition is known as "fatty infiltration," which is produced by excessive diet, especially if rich in fat and carbohydrate, and diminished oxidation from want of exercise. Various factors contribute; thus beer-drinkers are particularly prone to excessive deposit of fat, and the removal of the testis in the young male and the occurrence of the menopause in the female are frequently followed by obesity. In some individuals, moreover, although the constituents of their diet may be correctly balanced and there may be no lack of exercise, fat is developed to an abnormal extent. This has been ascribed by Cohnheim to a deficiency of energy or of activity of the cells.

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[1] Hamilton, *Text-Book of Pathology*, vol. i, p. 170.

Animal fats consist of varying mixtures of tristearin, tripalmatin, and triolein; in solid fats (*e. g.* tallow) the two former predominate. Human fat contains 70–85 per cent. of triolein.

Fat is soluble in ether and in xylol and gives characteristic reactions with certain reagents. Osmic acid, one of the most generally used, gives a black with some, but not all, forms of fat; apparently the staining is limited to triolein. Much better reagents are Sudan III, and Scharlach R, anilin dyes which stain fat a red colour; these may be applied to the fresh tissues or after hardening in formalin. Microscopically, fat appears as rounded, structureless, clear, highly refractile globules.

When fat is present in quantity, feathery crystals sometimes separate out, which have been described as consisting of margaric acid, but this is doubtful. In fatty detritus crystals of cholesterin are common, and form rhombic plates, frequently with one angle missing, soluble in hot alcohol, ether, and chloroform and giving first a red and then a purplish colour with strong sulphuric acid (acid 5 parts, water 1 part).

Fatty deposits are principally seen in the subcutaneous tissues, particularly of the abdomen, in the liver and bone-marrow, and about the heart. The condition may be general as in lipomatosis and obesity, or local as around contracted kidneys and in the muscles in pseudo-hypertrophic paralysis. A localised new formation of fat is known as a lipoma (which see). In fatty infiltration there is no disintegration of the protoplasm of the cells; the fat is produced in small droplets, which usually coalesce into large drops; these may distend the cells and cause atrophy of the protoplasm from pressure, but there is no evidence of fatty change of the protoplasm itself; the cell is normal save for the deposit of fat. It is true that in certain instances there may be a difficulty in deciding whether the lesion is fatty infiltration or degeneration.

Adiposis dolorosa, **"maladie de Dercum," is an extraordinary condition in which there are large deposits of fat in the lower extremity from the thigh to the ankle. It is almost confined to the female sex and is associated with trophic and mental disturbance. It is supposed to be an intoxication, and the thyroid gland and pituitary body have been found diseased, but the real pathology is quite unknown.**

Fatty degeneration, or metamorphosis, is another process in which fat appears in abnormal situations or in abnormal amount. It differs from fatty infiltration in that the cells containing the fat are primarily and notably damaged and degenerate. Fatty degeneration occurs as a result of (1) a deficient supply of nutriment to the cells, (2) interference with the nerve-supply to the part, "trophic influences," (3) disuse, (4) the action of poisons, and (5) the action of microbial toxins. In certain instances it is physiological, as, for example, in involution of the uterus after parturition, and in the cells of the ruptured Graafian follicle. Fatty degeneration is met with in pernicious anæmia (in the heart), in poisoning with phosphorus, carbon monoxide, arsenic, and mineral acids, and in chronic alcoholism, from the action of a high temperature (hyperthemia), in the heart from partial occlusion of the coronary arteries, and from the action of such microbial toxins as the diphtheria toxin. In fever, fatty degeneration is frequent, and is caused partly by the high temperature and partly by the action of the toxins which induce the fever. In the nervous system, the myelin of nerve-fibres severed from their trophic centres undergoes fatty metamorphosis, the fat probably being derived from lecithin, and this change forms the basis of the histological methods employed to demonstrate nerve-degeneration. Muscle-fibres separated from their trophic centres, or as the result of disuse, likewise undergo fatty degeneration. Hypertrophied tissues, such as muscle, are especially prone to fatty degeneration, also the cells in inflammatory conditions and in new growths.

Microscopically, in fatty degeneration the fat is seen as multiple minute droplets in the cells of organs or fibres of muscles. These minute droplets remain as such, or form many small droplets; they rarely coalesce into the larger drops seen in fatty infiltration. This is true for most tissues, but in the renal epithelium and liver-cells the fat may form either small or large drops, and it may be difficult, particularly in the latter, to decide whether the condition is fatty infiltration or fatty degeneration.

Macroscopically, tissues affected with fatty degeneration become paler, especially muscle, and often mottled; in advanced cases yellowish, flabby, and easily torn. In arteries milky patches may be noticed. The "arcus senilis" of the cornea seems to be a deposit of fat or of colloid in the lymph-spaces of the cornea (it was formerly regarded as fatty degeneration of the cornea).

Fatty degeneration is generally ascribed to a metamorphosis or transformation of the protoplasm or cellular proteids into fat, and the results of various experiments have been adduced in support of this view. Thus if a starving animal, in which all the reserve fat has disappeared, be poisoned with phosphorus, fatty degeneration ensues just as in a normal animal; and, moreover, the urea output is increased, showing that there is increased destruction of proteid. Pettenkofer and Voit fed dogs on lean meat containing a minimum of fat, and found all the nitrogen, but only a portion of the carbon, in the excreta, and argued, therefore, that part of the proteid had been converted into fat. In bodies buried for a long period there is frequently an abundant formation of *adipocere*—a mixture of fatty acids, and ammonia and lime soaps, supposed to be derived from cell proteids. The pathogenesis of fatty degeneration has, therefore, been ascribed to a transformation of the cell proteids into fat under the influence of the lowered vitality of the cells. In anæmia there is deficient oxygenation; this is also present in carbon monoxide poisoning, since CO replaces O in hæmoglobin, and deficient oxygenation means deficient nutrition and lowered vitality (in pernicious anæmia there can be little doubt that toxins play a part). Phosphorus poisoning also diminishes oxidation, the oxygen intake and carbonic acid output being lessened, but exactly how it brings about fatty degeneration is uncertain. Gaule states that the cell-nuclei are attacked, while Mott suggests that tissue respiration is interfered with. But these theories and explanations break down in the light of recent research.[1] Pflüger has shown that Pettenkoffer and Voit's results are founded on miscalculations, Rosenfeld that in phosphorus poisoning there is a transportation of fat from fat depôts, and not a transformation of the proteids of the liver-cells. If the *whole* of the reserve fat in a starving animal be used up, no fatty degeneration of the liver-cells ensues, and as regards adipocere bacterial action must be a factor in its formation.

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[1] See a good *résumé* by Christian, *Bull. Johns Hopkins Hosp.*, vol. xvi, No. 16, 1905, p. 1.

With regard to the apparent disappearance of fat during starvation, it must be remembered that fat comes to the tissues in a soluble and non-molar condition, and therefore, though it cannot be detected macroscopically or microscopically, this is no proof that it really is absent.

Athanasiu and Taylor investigated experimental phosphorus poisoning in frogs. The frogs were divided into two groups, each of which had the same number of frogs and the same total weight; to one group phosphorus was given, the other was kept as a control. When a phosphorised frog died, a control frog of equal size was killed, and the total amount of fat in each animal estimated. The amount of fat in each was found to be the same, although the liver of the phosphorised frog was fatty—pointing to a redistribution, not to a new formation, of fat.

It is believed that fat may be formed from carbohydrates; and it is generally admitted that glycogen and carbohydrates can be derived from proteids, that certain proteids, "glycoproteids," possess a carbohydrate radicle, and the indirect formation of fat from cell proteids is therefore a possibility, but it would certainly seem that fatty degeneration as ordinarily met with is due to a redistribution of fat in the body, the deposition of the fat in the cells seriously damaging their integrity, in which respect fatty degeneration differs from fatty infiltration. Or possibly, in fatty degeneration there is a deposit of fat in previously damaged cells.

PIGMENTATION.—Alterations in pigmentation are very common. Increased pigmentation may be due to excessive formation of the pigment normally present as yellowish, brownish, or black granules in the cells of fibrous and epithelial tissues. This is *autochthonous* or *metabolic pigmentation* and is met with markedly in Addison's disease, in pregnancy, and in freckle-formation. The greatest degree of pigmentation occurs in pigment moles and in certain new growths (melanotic sarcoma). The pigment usually lies within the cells.

Purple or red birth marks, port-wine stains, etc., are nævoid in nature.

Hæmatogenous pigmentation arises from the deposition of pigment derived from hæmoglobin. This is well seen after hæmorrhages, as in the familiar black eye. The changes occurring in extravasated blood will be mentioned later (p. 250). Excessive destruction of blood, as in septic intoxication, pernicious anæmia, malaria, and by certain poisons, *e.g.* potassium chlorate, anilin, etc., may give rise to pigmentation of the leucocytes, as in malaria, and of the organs, *e. g.* the liver and spleen in malaria, and the liver in pernicious anæmia.

Certain pigments of obscure origin may make their appearance under some circumstances, *e.g.* yellowish ones in the skin in xanthoma and in the corpus luteum of the ovary, and greenish ones in the lymphomatous new formations of chloroma.

Biliary pigmentation occurs in icterus or jaundice and stains the various tissues and secretions yellow, also in many infections and intoxications, such as typhoid, septicæmia, yellow fever, and from the action of certain poisons. This will be referred to again when jaundice is discussed.

Extraneous pigmentation may result from tattooing, in which a pigment is introduced through scratches or punctures in the skin, from the *inhalation* of particles such as coal-dust, as in the *miner's lung,* and from the absorption of substances by the alimentary tract, particularly silver salts, the long-continued administration of which produces a general and permanent greyish discoloration (*argyrosis*), and to a slight extent lead, which gives rise to a blue line in the gums.

Absence of normal pigmentation may occur congenitally, as in *albinism*, or may be acquired, as in *leucoderma*, a skin affection.

INFILTRATION WITH SALTS.—Petrification or incrustation is not infrequent, and consists in a deposition in the tissues of salts, generally calcium carbonate and phosphate with a small quantity of magnesium salts. Calcareous deposition may be a normal process, as in the formation of bone, in which the deposit occurs as minute granules; and pathologically a similar deposit may take place in necrotic tissues, as in caseous tuberculous glands, dead parasites, thrombi, dead fetuses (*lithopædia*), or in tissues the nutrition of which has been seriously interfered with, as in tumours and in the tunica media of arteries. Calcification, although mainly affecting the fibrous constituents, may also invade cells such as ganglion cells and renal epithelium. In the early stages the change cannot be recognised with the naked eye, but later the tissues affected become whitish and dense and ultimately of a stony hardness, without any alteration in form. Chalky concretions may also occur, particularly in tissues the subject of chronic inflammation.

Urates, chiefly urate of soda, become deposited in the tissues in gout, in the cartilage of joints, particularly the metatarso-phalangeal of the big toe, and as nodules in ligaments and cartilages of joints, in the pinna of the ear (*tophi*), and between the kidney tubules. The sodium urate, microscopically, appears as sheaves of fine needle-shaped crystals.

CALCULI or stones are formed by the deposition of salts on some nucleus or matrix, which may be composed of crystals, desquamated cells, fibrinous coagula, flakes of mucus, colloid granules, bacteria, or foreign bodies. Calculi are met with in the ducts of glands or in cavities lined with mucous membrane, and may cause inflammation, or obstruction to the excretion. The most important calculi are gall-stones, composed of cholesterin, bile-pigments, or calcium carbonate; urinary calculi, composed of uric acid, urates, phosphates, calcium oxalate or carbonate, and rarely of cystin or xanthin; salivary and pancreatic calculi, composed of lime salts; and fæcal calculi, composed of inspissated fæces and lime salts.

Cysts are cavities of pathological formation, provided with a definite membrane enclosing fluid or semi-fluid contents, and secondary to certain pathological processes. A cyst must be distinguished from a *cystoma*, which is a primary pathological new formation or tumour, arising from active proliferation of a matrix, and enclosing cystic spaces.

Retention cysts are of common occurrence and result from the blocking of a duct of a gland so that the secretion cannot escape, as in sebaceous glands (*wen*), and in the mamma, kidney, ureter, pancreas, salivary glands (*ranula*), etc.; from excessive secretion into a closed space, as in the thyroid, tendon sheaths (*ganglion*), bursæ, and Graafian follicles, or into a vestigial structure such as a cervical fistula or the Wolffian body or Müllerian ducts. The latter have been termed "tubo-cysts" by Sutton.

Disintegration cysts are due to softening and disintegration, and are met with in the brain after hæmorrhage, and in tumours.

Parasitic cysts are due to the presence of parasites with vesicles, such as the hydatid or echinococcus cyst.

Dermoid cysts are congenital and are discussed elsewhere. Cysts may also form round foreign bodies.

CHAPTER III.

NEOPLASMS, TUMOURS, OR NEW GROWTHS—THEIR CLASSIFICATION AND GENERAL CHARACTERS—THE NON-MALIGNANT NEOPLASMS—THE MALIGNANT NEOPLASMS—THE GENESIS OF NEOPLASMS.

NEOPLASMS, TUMOURS, OR NEW GROWTHS.

It is difficult exactly to define what is meant by a neoplasm or tumour. On the one hand a neoplasm merges into hypertrophy and hyperplasia, on the other into inflammatory new formations. It differs from the former, however, in that the new tissue is different from the matrix tissue; it is distinguished from the latter by its mode of genesis and by the variety of types that may be assumed. It is a new formation of tissue, atypical in structure, of aberrant and irregular growth, and subserves no useful purpose.

The term "tumour" is used in different senses clinically and pathologically. Any swelling is clinically a tumour, *e.g.* an aneurysm, or a cyst formed by the occlusion of a duct. Pathologically, a tumour always includes the conception of a new formation of tissue. It is preferable, therefore, to employ the term "neoplasm" in place of "tumour" in a pathological sense. Neoplasms are of varying size, form, and structure. Some grow slowly, others rapidly; some are distinctly marked off from the surrounding tissues, others grow into, infiltrate, and invade the tissues. Some are single, others multiple; and others, while starting from a single centre, have the capacity of reproducing their like in distant parts of the body; these secondary neoplasms derived from the primary ones are known as the *secondary* or *metastatic growths.*

The consistence of neoplasms varies considerably. Some are hard and fibrous, others soft and cellular; and there is a considerable tendency for all to undergo retrogressive changes—hyaline, colloid, or fatty degeneration, calcification, necrosis, and ulceration; these occur mainly in the older parts of the growth. In some cases neoplasms atrophy from interference with their blood-supply, or sometimes without appreciable cause. Clinically, neoplasms are divided into benign or non-malignant and malignant, but there is no distinct line of demarcation between the two. The benign neoplasms are usually sharply defined from the surrounding tissues and are encapsuled, grow slowly, do not recur after complete removal, do not form secondary growths, are single, and do not endanger life except by reason of their size and situation. Malignant neoplasms, on the other hand, are not sharply defined and have no capsule, and hence it is difficult to remove them completely and they tend to recur; they grow rapidly as a rule, and owing to secondary growths may be multiple, and they tend to destroy tissue and ultimately to cause death. There are exceptions to all these characteristics; thus, benign fibromata and lipomata are frequently multiple, a lipoma may not be encapsuled, some forms of sarcoma are slow to form secondary growths, and so on. Another peculiarity of the malignant neoplasms is the production of a cachexia, which may be due partly to the formation of toxic substances, partly to abstraction of nutriment, and such growths are often rich in glycogen.

In addition to being divided into benign and malignant, neoplasms may be classified according to the kind of tissue which mainly constitutes them, *e.g.* fibroma, of fibrous tissue; lipoma, of fat, etc., and according to the embryonic layer from which they are derived, viz. the mesoblast, epiblast, and hypoblast.

A great variety of classifications have been formulated, one of the best, perhaps, being that suggested by Powell White,[1] which is as follows:

(A) ORGANOMATA OR ORGAN TUMOURS.—In these distinct organs or parts of organs are present, *e. g.* the dermoid.

(B) HISTIOMATA OR TISSUE TUMOURS.—In these distinct tissues are present, which, however, are not arranged to form organs.

(a) *Connective-tissue tumours* (*desmomata*).—Fibrous tissue, *fibroma*; fat, *lipoma*; mucous tissue, *myxoma*; cartilage, *chondroma*; bone, *osteoma*; neuroglia, *glioma*.

(b) *Lymphoid tissue tumours* (*lymphomata*).—Lymphadenoid tissue, *lymphadenoma* or *lymphoma*; bone-marrow, *myeloma*.

(c) *Muscle tumours* (*myomata*).—Smooth muscle, *leiomyoma*; striated muscle, *rhabdomyoma*.

(d) *Nerve-tissue tumours* (*neuromata*).—Medullated nerve tissue, *myelinic neuroma*; non-medullated nerve tissue, *amyelinic neuroma*.

(e) *Epithelial tissue tumours* (*epitheliomata*).—Squamous epithelium, *squamous adenoma* and *papilloma*; columnar epithelium, *columnar adenoma* and *papilloma*; spheroidal epithelium, *spheroidal adenoma*; endothelium, *angeioma* and *endothelial papilloma*.

(C) CYTOMATA OR CELL TUMOURS.—In these cells make up the main bulk of the neoplasm (at least in the growing portions), and are not arranged to form any tissue.

(a) *Tumours of indifferent cells* (*blastoma*).—Tumours, some of the cells of which seem to be able to form epithelium, others to develop into connective tissue, as in certain tumours of the parotid and kidney, which do not appear to be either carcinomata or sarcomata.

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[1] *Lancet*, 1902, vol. i, p. 423.

(b) *Tumours of connective-tissue cells, also of lymphoid tissue and muscle* (*sarcomata*).—(1) Pure sarcomata, *round-*, *spindle-*, and *giant-celled*; (2) compound sarcomata, *fibro-*, *chondro-sarcoma*, etc.

(c) *Tumours of epithelial cells* (*carcinomata*).—*Squamous*, *columnar*, and *spheroidal*, and *endothelial carcinoma*.

This classification cannot be accepted in its entirety; for instance, there is a difficulty with regard to the blastoma, though there is not at present, perhaps, such a tendency absolutely to separate the different embryonic layers that there used to be, neuroglia is epiblastic in origin, and "endothelial carcinoma" is a curious term. The application of the term "epithelioma" to non-malignant epiblastic and hypoblastic neoplasms is a convenient one, and is employed by Ziegler, but the name "epithelioma" is also given clinically and pathologically to various forms of carcinoma. "Cancer" is applied colloquially to any form of malignant neoplasm, and may conveniently be used in this sense, but it is often used clinically and pathologically to denote a carcinoma.

The various forms of neoplasms may now be described, dividing them for this purpose into non-malignant and malignant, after which the genesis of neoplasms will be considered.

THE NON-MALIGNANT NEOPLASMS.

Fibroma.—A fibroma is a neoplasm composed of connective-tissue cells and fibres resembling more or less closely those occurring in ordinary fibrous tissue.

Characters.—The tumour may be hard or soft according to the denseness of its component tissues, amount of œdema fluid it contains, and association of degenerative changes, especially myxomatous. It is more or less rounded, or may be lobulated, sometimes polypoid, and generally encapsuled, and whitish or greyish in colour. It does not grow again if thoroughly removed, but if a portion be left the growth may recur.

Situation.—Fibromata occur in any organ or structure containing connective tissue, but are commonest in the skin (the pendulous cutaneous fibroma is known as *molluscum fibrosum*), fasciæ, periosteum, tendons and tendon sheaths, nerves (*neuroma*), uterus, and breast.

Structure.—The fibroma consists of connective-tissue cells and fibres, the former being relatively more abundant in the soft fibromata. The cells are elongated and spindle-shaped, the fibres are white fibrous tissue, generally less wavy than in ordinary connective tissue, with a small proportion of yellow elastic fibres, and there is a general tendency to the formation of whorls. The vessels are generally scanty, being more numerous in the early, rapidly-growing stage, and are of a normal type. It may be difficult to distinguish a fibroma from a fibrous hyperplasia. Various combinations of the fibroma with other tissues occur, *e. g.* the fibromyoma.

NEUROMA.—Strictly the term "neuroma" should be reserved for a neoplasm consisting of proliferated nerve-fibres or cells; but such are very rare, and it is commonly applied to new growths, generally of fibrous tissue, *i. e.* fibromata, entangling nerve-fibres and cells (*false neuroma*). These are most frequently seen after amputations, when the ends of the nerves become involved in fibro-cicatricial tissue. In other cases the growth may arise from the perineurium, or endoneurium, or sheath of the nerve, the nerve-fibres becoming stretched over it.

GLIOMA.—The glioma is a neoplasm of the central nervous system and retina arising from the neuroglia. It is rarely of large size, is single or multiple, and is greyish, pinkish, or reddish in colour according to the number of vessels contained in it. Microscopically, it consists of glia cells—cells with large round or oval nuclei and scanty cytoplasm and having several delicate fibrils which branch and interlace with their neighbours. The relative abundance of cells and fibres is subject to much variation, and varying amounts of nerve-fibres and cells may be incorporated in the tumour.

MYXOMA.—Strictly, the myxoma is a neoplasm composed of mucoid tissue and is rare, but occurs in the subcutaneous tissue. It consists of a delicate network of fibres, at the intersections of which are branching cells with dark staining nuclei and fair amount of cytoplasm. Commonly the term is applied to an œdematous fibroma, such as the mucous polypus so common in the nose. This consists of a delicate fibrous tissue with a few cells containing œdema fluid in its interstices and covered with ciliated epithelium (Plate I., A.). The œdematous fibroma also occurs in the intestine and uterus.

LIPOMA.—The lipoma is a neoplasm composed of adipose tissue.

Characters.—Usually circumscribed and lobulated, often multiple, somewhat doughy in consistence, and may attain large size. In some instances the growth is more or less diffuse and uncircumscribed, particularly under the chin and at the back of the neck. On section it presents the ordinary appearance of fat.

Situation.—Particularly frequent in the subcutaneous tissues of the shoulders, neck, back, axillæ, and groin, also in connexion with the abdominal viscera, etc.

Structure.—Microscopically, the tumour has the ordinary structure of fat or adipose tissue, but may contain more fibrous tissue than normal adipose tissue.

The XANTHOMA is a yellowish neoplasm occurring on the eyelids and, structurally, is an embryonic adipose tissue.

CHONDROMA.—A chondroma is a neoplasm composed largely or entirely of cartilage.

Characters.—Usually small and nearly spherical, sometimes large and nodular or irregular, frequently multiple, generally encapsuled, hard, and on section presenting the appearance of cartilage. The larger tumours may contain softened foci, or even cystic cavities filled with a gelatinous material. Chondromata are apt to become malignant (*chondro-sarcoma*), and are most frequent in young adults.

Situation.—Arises in connexion with cartilage (*ecchondrosis*), *e. g.* from the nasal septum, larynx, or ribs, or in regions where cartilage is normally absent (*enchondroma*), *e. g.* the fully-developed bones, parotid gland, testicle, and mamma.

Structure.—Microscopically, the chondroma usually consists of hyaline cartilage with a variable proportion of cells, but sometimes the matrix is fibrillated like that of fibro-cartilage. In bone the chondroma may with justice be assumed to arise from misplaced islets of cartilage, but in other regions misplacement of embryonic remnants offers the only explanation. In the parotid it may be assumed to arise from Meckel's cartilage of the branchial arches.

OSTEOMA.—The osteoma is a neoplasm composed of osseous or bony tissue, compact or ivory, or spongy or cancellous. It must be distinguished from hyperplasia of bone, *e. g.* the callus formed during the repair of a fracture, and also from calcification, which may occur in almost any tumour.

Characters, etc.—Osteomata are frequently multiple and usually arise in connexion with bone. A small outgrowth from a bone is known as an *exostosis*; the bony outgrowths in the neighbourhood of the joints of long-bones are known as *osteophytes,* and are, perhaps, inflammatory. The compact varieties are generally small, but the cancellous ones may attain large dimensions. To osseous tumours arising in connexion with the teeth the general term of *odontoma* is applied.

MYOMA.—The myoma is a neoplasm composed of muscle, the *rhabdomyoma* of striated muscle, and the *leiomyoma* of plain muscle, but is rarely wholly composed of muscle. The *rhabdomyoma* is a rare tumour, the commonest seat being in the kidney, less frequently the skeletal muscles. It is usually described as being sarcomatous, but this appearance, due to the large numbers of embryonic cells present, is ascribed by Ohlmacher to the fact that the myomatous tissue never reaches its full development of striated muscle. The growth generally consists of a vascular connective-tissue framework containing large numbers of round and spindle cells and a small number of more or less developed striated fibres.

The *leiomyoma* is most familiar as the uterine "fibroid." It may attain large dimensions and may be single or multiple. The tumour is firm, rounded, or lobulated, and is also occasionally found in connexion with the intestine, bladder, etc. Microscopically, it consists of masses of elongated spindle-shaped plain muscle-cells, usually with more or less admixture of fibrous tissue; *i. e.* the growth is strictly a fibro-myoma (Plate XXII., A., p. 460).

Lymphoma. — Whether there is really a neoplasm composed of lymphoid elements is doubtful, but the term "lymphoma" is applied in a general sense to tumours having a lymphoid-like structure. Thus in leukæmia masses of lymphoid tissue are found in the spleen and other organs (see p. 236). In other cases there is a lymphoid hyperplasia, as in lymphadenoma and Hodgkin's disease (see p. 242). In others, again, the growth is a lympho-sarcoma or small round-celled sarcoma.

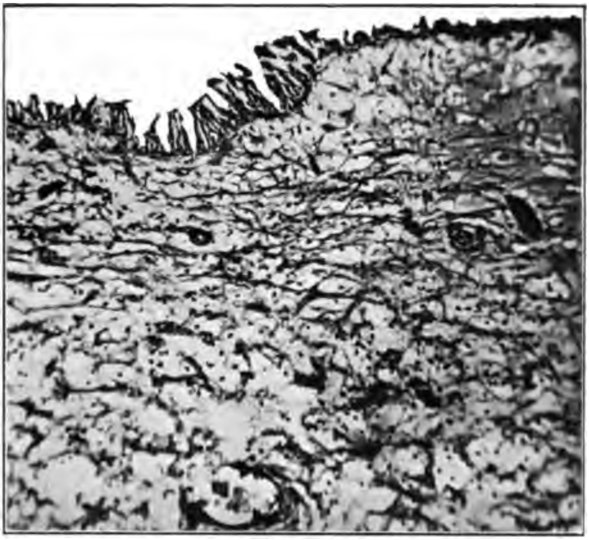
Angeioma.—The angeioma is a neoplasm in which vascular elements preponderate. The term is commonly used to denote a blood-vascular tumour or "hæmangeioma," but lymph-vascular tumours or "lymphangeiomata" also occur. Strictly speaking, all vascular tumours produced merely by the dilatation or overgrowth of pre-existing vessels should be excluded from this group, but common usage sanctions some relaxation of this rule.

The hæmangeiomata present several varieties.

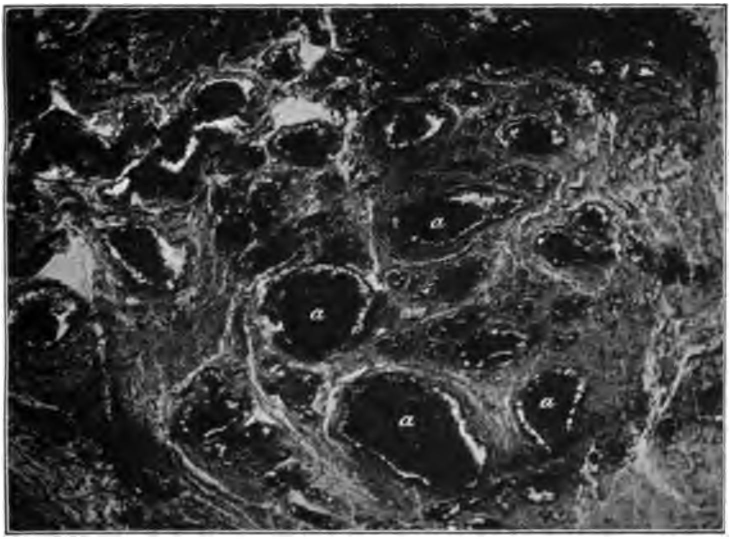
The *simple angeioma* is made up of a basement tissue in which are an abnormal number of distended veins and capillaries. It is commonly seen in the skin, and forms the birth-marks, port-wine stains (*telangiectases*), and vascular *nævi*. Microscopically, the growth (it is hardly a tumour) is seen to be made up principally of capillaries in the course of which are fusiform dilatations, and the walls of which are in some instances considerably thickened. Another form of simple angeioma is the venous or varicose tumour, made up of dilated veins as in hæmorrhoids or piles.

The *cavernous angeioma* differs from the simple angeioma in that the tubular form of the vessels is lost and is replaced by wide, variously shaped spaces separated by fibrous septa, the walls of which are lined

PLATE I.



A. Œdematous fibroma of nose. (Hæmatoxylin and eosin, × 120.)



B. Cavernous angeioma of hand. *a, a, a.* Spaces filled with blood.
(Hæmatoxylin and eosin, × 50.)

To face page 48.

with endothelium (Plate I., B.). It occurs in the skin, forming a raised irregular patch, the ordinary *nævus*, and occasionally in the organs, particularly the liver.

The *lymphangeioma* may be cavernous or cystic, or it may be made up of a mass of dilated lymphatics (*lymphangiectasis*). The former appear to be the essential cause of macroglossia and macrocheilia (p. 330).

PAPILLOMA.—The true papilloma is strictly a neoplasm of the skin and reproducing the structure of the papillæ. The term is, however, often applied to any villous excrescence of an epithelial surface, as of the bladder.

A wart is a typical example of a cutaneous papilloma. It consists of an outgrowth of connective tissue containing blood-vessels and covered with stratified squamous epithelium. Similar growths, often more or less cauliflower-shaped, occur in the larynx (Plate II., A.). In the bladder and mucous membranes the papillomata are much softer and more vascular, and are covered with the variety of epithelium proper to the part.

A *callosity* is simply a localised collection of epidermal cells, and a *corn* is a papilloma on to which a callosity has been superadded.

A *keratoma,* or horn, is a localised accumulation of the horny layers of the epidermis and may reach a considerable length and sometimes arises in connexion with a sebaceous tumour. It usually occurs on the face or scalp.

The papillomata often develop in the course of chronic irritation, and in some cases are undoubtedly infective. They are to be classed as epithelial growths rather than fibromata, since if they undergo a malignant metamorphosis, a carcinoma is generally produced.

ADENOMA.—The adenoma is a neoplasm which tends to reproduce the structure of a gland or gland-like organ: that is, it has a tubular structure lined with columnar epithelium or an alveolar structure filled with spheroidal epithelium. In some instances the supporting connective tissue is thrown into folds which project into the lumina of the tubes or acini, forming the *papillary adenomata.* Adenomata generally arise in connexion with glands or pre-existing glandular organs, in the latter probably from misplaced rudiments, but occasionally independently of these. They are thus met with in the skin in connexion with the sebaceous glands, in the breast, in the prostate, in the kidney, in the intestine (in the rectum often forming "polypi"), and in the uterus and ovary (Plates XXII., B., and XXIII., B.).

The adenomata are usually of slow growth and rarely attain large size, but in the ovary particularly may grow rapidly and may attain huge dimensions. They are usually enclosed in a fibrous capsule, and though having a glandular structure, this is atypical; the acini are irregular in size, shape, and arrangement, and the connective-tissue stroma is generally present in amount greater than in a normal gland, and may be so abundant as to constitute a "fibro-adenoma," as in the breast (Plate XXIV., B.).

THE MALIGNANT NEOPLASMS.

(A) The Sarcomata.

The sarcomata are malignant neoplasms of the connective tissue type; *i. e.* they develop from tissues derived from the mesoblast, and hence for the most part grow in the connective tissues; but since in glandular and other epi- and hypoblastic tissues a mesoblastic stroma is present, they may occur also in these. They are usually classified according to the form and arrangement of their cells. Their size and rate of growth are very variable; their consistence, while usually soft, often markedly so, may be hard, as in the chondro- and osteo-sarcomata. Similarly, while an abundant development of blood-vessels is often a marked feature, it is not necessarily so. The blood-vessels in the stroma may, exceptionally, be histologically perfect, but usually they are mere channels lined with endothelium, or even, apparently, simply blood-spaces limited by the cells of the growth; lymphatics and nerves seem to be absent. The majority of the sarcomata tend to produce metastases, but not all, in this respect differing from the carcinomata. This is the case in the myeloid variety. The metastases in many instances may be very abundant, and generally reproduce the structure of the original growth. Dissemination takes place mainly by the blood-vascular system, but also by the lymph-channels.

Sarcoma, although it may occur at any age, is particularly prevalent in childhood and young adult life. Not infrequently it develops from birth-marks, nævi, moles, etc.

There is no peculiar character which differentiates the sarcoma-cell from other forms of cells, and though division by karyokinesis is the rule, direct division also occurs. Around each individual cell of the growth a more or less delicate connective-tissue stroma is considered to be present, which, though very apparent in some forms, is difficult to discern in others, but by teasing up the fresh tissue in salt solution and staining lightly with methylene blue it can generally be made out. Around the slow-growing varieties a more or less definite capsule is frequently present, separating the tumour from the surrounding tissues. Polymorphonuclear and mononuclear leucocytes are often seen in the tumours, and in the tissues near the growing margin plasma-cells and leucocytes are frequently present. As the tumours increase in size degenerative changes often ensue, such as mucoid and hyaline; hæmorrhage into the growth is a frequent event, and calcification, chondrification, and ossification occur.

ROUND-CELLED SARCOMA.—The round-celled sarcomata are usually described as small- and large-celled, but the two varieties merge into each other. The growths are generally soft and very cellular, grow rapidly, and are highly malignant, particularly the smaller celled and more cellular varieties.

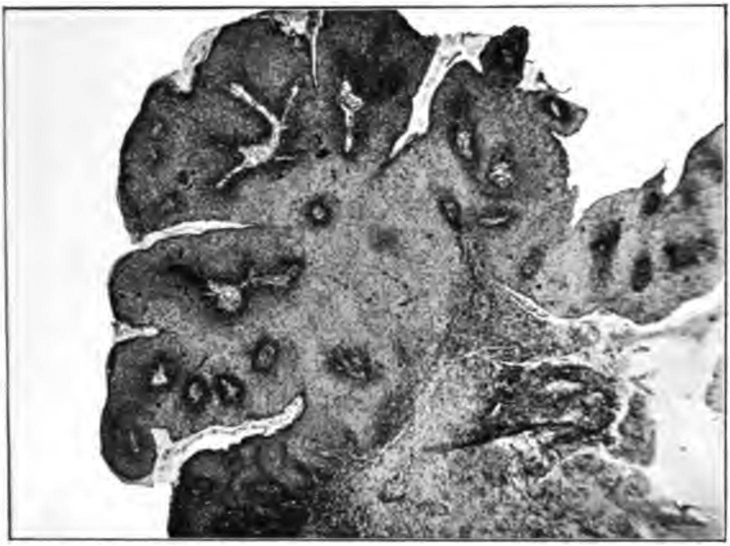
In the *small round-celled sarcoma* the individual cell is generally distinctly larger than a lymphocyte, to which it has most resemblance, the cells are numerous, and the intercellular substance scanty (Plate II., B.). This is one of the commonest varieties.

In the *large round-celled sarcoma,* which is not a common form, the cells have a big, round, distinct nucleus with abundant cytoplasm, so that they are large and distinct, larger than most of the normal cells of the body. The connective-tissue stroma is not well marked and never well developed; it always assumes an embryonic type.

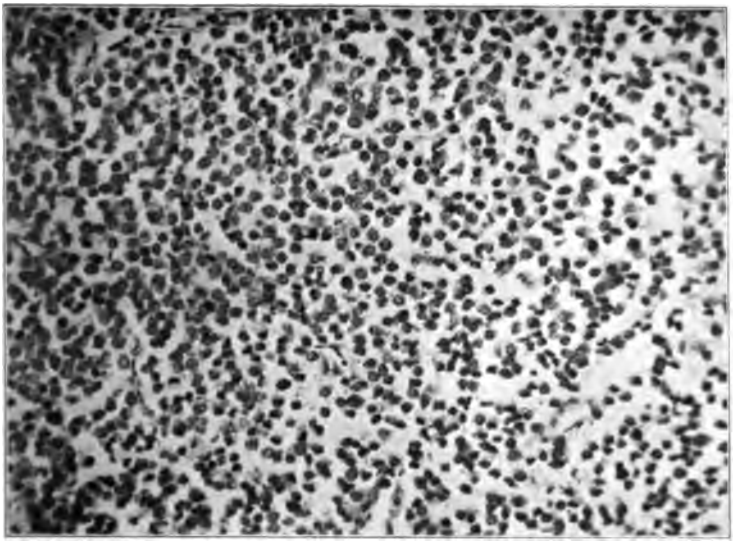
In some of the round-celled sarcomata there is a distinct reticulum like that of lymphadenoid tissue, and the whole structure resembles that of a lymphatic gland. To these the name "lympho-sarcoma" has been given, though the difference between it and other small round-celled forms is often not very distinct; the term "lympho-sarcoma" is sometimes applied to Hodgkin's disease, but this seems to be a disease *sui generis* and not sarcomatous (see p. 242). The *chloroma* is probably a round-celled sarcoma (see p. 236).

SPINDLE-CELLED SARCOMA.—This is one of the com-

PLATE II.



A. Papilloma of the larynx. (Hæmatoxylin and eosin, × 25.)



B. Round-celled sarcoma. (Hæmatoxylin and orange-rubin, × 150.)

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monest varieties, growing from connective tissue, fascia, periosteum, etc. Large- and small-celled varieties may be distinguished. The cell in this form is elongated and spindle-shaped, tapering at each end to a point, and not infrequently bifurcated at the extremities. The nuclei are also elongated, and not unlike the nuclei of unstriped muscle. The cells and stroma tend to arrange themselves in whorls as in a fibroma. The connective-tissue stroma varies in amount; in some it is abundant and reaches a high degree of development, almost into well-formed fibrous tissue. To tumours of this class the name *fibro-sarcoma* has been applied; they grow slowly and are but slightly malignant. The *oat-celled sarcoma* is another variety, so called on account of the shorter, oat-shaped cells of which it is composed. Often there is a mixture of round cells with small and large spindle cells, *mixed-celled sarcoma.* The blood-vessels in the spindle-celled sarcoma vary in amount, and are often little more than endothelial tubes.

The stroma may undergo mucoid degeneration, giving rise to the *myxo-sarcoma,* and calcification or ossification may occur.

MYELOID SARCOMA.—The myeloid or giant-celled sarcoma is met with especially in connexion with the periosteum or bone-marrow, and occurs most commonly in the maxillæ and femur. The growth consists of round or spindle-cells, or both, arranged round giant cells containing many nuclei (Plate III., A.). The giant cells are generally somewhat ovoid in shape, with irregular contour; the nuclei may be few or many, sometimes very numerous, but have as a rule no particular arrangement in the cell. Secondary growths are very rare, and on this account some authors have excluded this neoplasm from the sarcomata and have assigned it a place of its own, terming it a *myeloma.*

duced. It would be preferable to limit the term "alveolar," if it be used at all, to this type, and to speak of an "alveolar spindle-celled sarcoma," etc.

ENDOTHELIOMA.—The term "endothelioma" has given rise to much controversy. It is applied to neoplasms which histologically resemble carcinomata, but which, since they arise from mesoblastic structures, must be included among the sarcomata. As their name implies, they arise from endothelial cells and hence are found in connexion with serous membranes, blood-vessels, perivascular lymph-spaces and lymphatics, and extend by these vessels. Many of the alveolar sarcomata belong to this group, while the close resemblance of endothelium to epithelium has caused others to be classed with the carcinomata.

The cells of the neoplasm are round and flat, or spheroidal, "epithelioid" in appearance, and they form nests or groups in alveoli composed of a more or less well-defined fibrillar stroma. Tumours of this type with a columnar arrangement of cells which have undergone hyaline degeneration have been termed *cylindroma*. In the dura endothelial tumours with an abundant fibrous stroma and containing calcareous granules have been termed *psammomata* (Plate IV., A.); these are, however, sometimes round-celled sarcomata. The mixed tumours of the parotid are regarded as endotheliomata (see p. 332).

The endotheliomata are often of slow growth, and show little tendency to invade the neighbouring tissues or to produce metastasis.

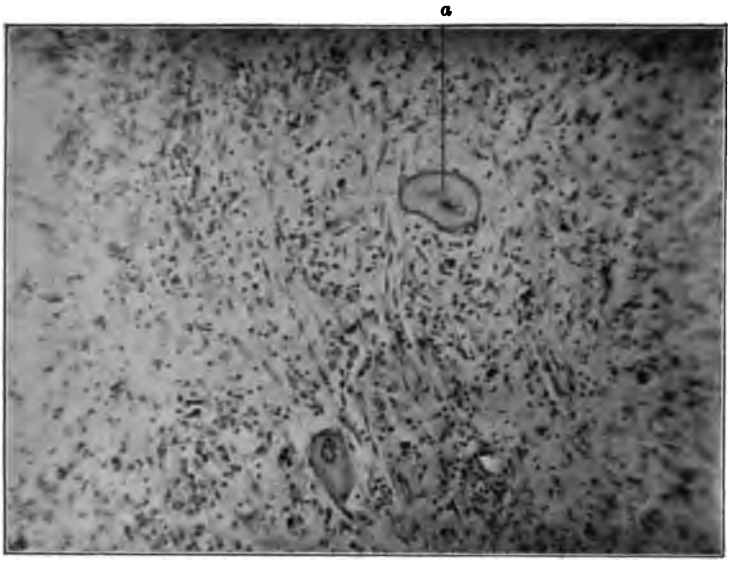
(B) The Carcinomata.

The carcinomata are an important group of malignant neoplasms which develop from tissues derived from the epiblast or hypoblast. At the same time, they contain a stroma of mesoblastic origin which proliferates and helps to form the new growth *pari passu* with the proliferation of the epithelial elements.

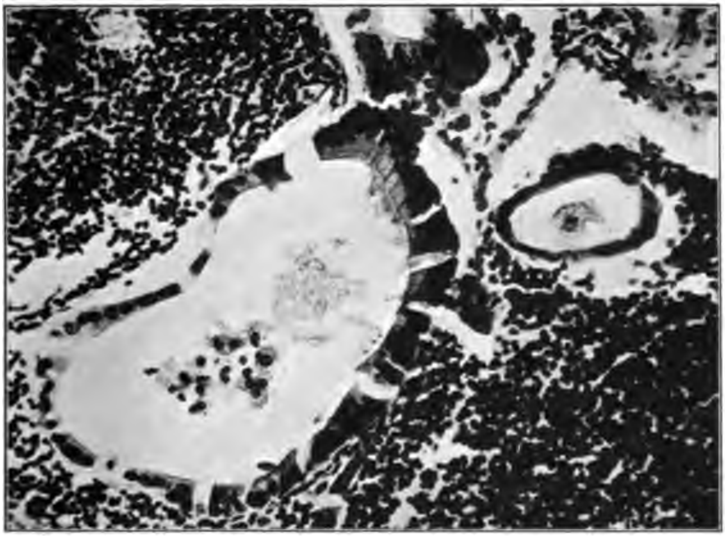
For the rare instances in which a primary carcinoma develops in a purely mesoblastic tissue the embryonic misplacement of epithelial elements is the only satisfactory explanation.

The carcinoma invades in a marked manner the tissue or organ in which it is growing, and secondary growths or metastases are a prominent feature. These are conveyed mainly by the lymphatics, much less frequently by the blood-vessels. The cells resemble some form of epithelial cell—there is no such thing as a peculiar "cancer cell"—and vary much in abundance. The cells of the neoplasm are generally like the cells from which they are derived—*i. e.* squamous cells beget squamous cells, columnar cells columnar cells, and so on; but oçcasionally one variety of cell may pass into another; *e. g.* a columnar-celled carcinoma of the cervix may become squamous-celled, particularly if there be prolapse of the uterus and the growth project from the vulva. Moreover, the type and arrangement of cell of the primary growth are reproduced in the metastases (Plate IV., B.). The stroma consists of a more or less perfect connective tissue containing blood-vessels and lymphatics, and possibly nerves. The relative proportion of stroma and cells determines the hardness of the tumour and its rate of growth; the less the amount of stroma and the more abundant the cells, the softer is the tumour and the more rapid its growth. To a carcinoma relatively rich in cells the term *encephaloid* is applied, to one relatively rich in stroma, *scirrhous*. The manner of development of the connective-tissue stroma is a difficult problem, and whether its proliferation precedes or succeeds the epithelial proliferation is a debated point.

PLATE IV.



A. Psammoma of the brain, showing two calcareous granules, *a*. (Hæmatoxylin and orange-rubin, × 45.)



B. Metastatic growth in lymphatic gland secondary to rectal carcinoma. The columnar-celled type is reproduced in the secondary growth. (Hæmatoxylin and orange-rubin, × 120.)

To face page 56.

Leucocytes, small and large mononuclear, polymorphonuclear, etc., and plasma cells, are often present in the growths, and a round-celled infiltration envelops the growing border.

Carcinoma is liable to undergo various retrogressive changes, fatty, hyaline, mucoid and colloid, and occasionally calcification. Carcinoma is particularly frequent in the female in the genital organs and mamma, in the male in the lips and tongue. As regards other regions there is not much difference in incidence between the two sexes.

To many forms of carcinoma the name "epithelioma" is frequently given, *e. g.* squamous epithelioma, but since this term is now being applied to all epithelial neoplasms, non-malignant and malignant, it is preferable to designate the malignant epithelial neoplasms as carcinomata.

SQUAMOUS-CELLED CARCINOMA.—This variety is met with in regions normally covered with epithelium of the squamous type, *e. g.* the skin, buccal cavity, and tongue, pharynx, larynx, and œsophagus, and anus. As already mentioned, carcinoma of other types is occasionally transformed into the squamous-celled. The neoplasm produces warty or nodular growths, spreading widely from the starting-point, and generally breaking down and ulcerating in the older parts. Microscopically, the growth is composed of a parenchyma of flattened, spheroidal, and polygonal cells in clusters or groups, and arranged more or less concentrically (Plate V., A.). These are surrounded by a stroma more or less rich in cells. In the younger portions of the growth the epithelial cells are for the most part spheroidal, and the stroma abundantly cellular with imperfect fibrillæ. In the older portions the cells become flattened, tend to undergo keratinisation, and frequently become concentrically arranged, forming the "cell-nests" (Plate V., B.), which may undergo almost complete keratinisation with the formation of the so-called "epithelial pearls." The masses of epithelium have no particular shape, and often form columnar or irregular outgrowths or processes, ovoid or round in section, from the main mass at the growing margin, at which there are collections of round and plasma cells. "Prickle cells" are well seen, as in normal epithelium. In the older portions the stroma may attain a coarse dense fibrous character similar to that of cicatricial tissue. Cell nests are only exceptionally seen (*e. g.* in the buccal cavity and tonsils) in tissues other than carcinoma, and hence are of considerable diagnostic importance.

RODENT ULCER.—The rodent ulcer or cancer, histologically, has many of the characters of the squamous carcinoma, but at the same time many points of difference. It affects the skin, particularly of the face and scalp, the commonest seat being the neighbourhood of the outer canthus of the eye,[1] and spreads locally, superficially at first, but ultimately may lead to great destruction and fearful disfigurement. A remarkable and unexplained feature, and one that differentiates it almost absolutely from squamous-celled carcinoma, is that it has no tendency to produce metastases, so that complete removal means cure.

Microscopically, the rodent ulcer consists of masses of epithelium having a general resemblance to those of squamous-celled carcinoma, but the cells tend to be more regular, more ovoid, and smaller. The outgrowths, or processes, are also in section smaller and more angular than those of the squamous carcinoma. Lastly, cell nests are never, or hardly ever, seen (Plate VI., A.).

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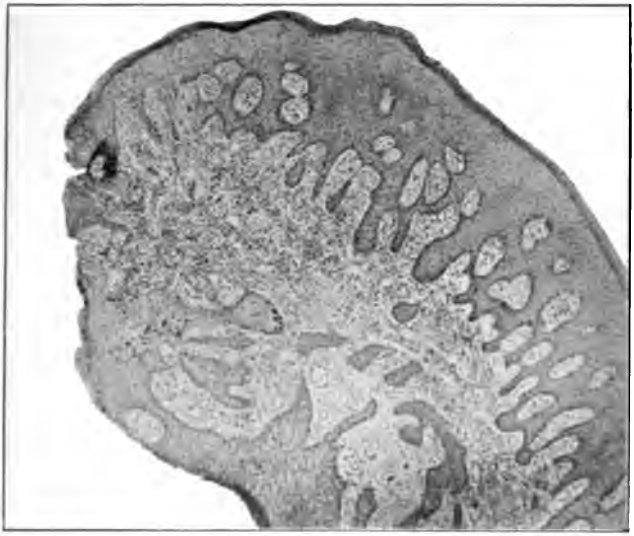
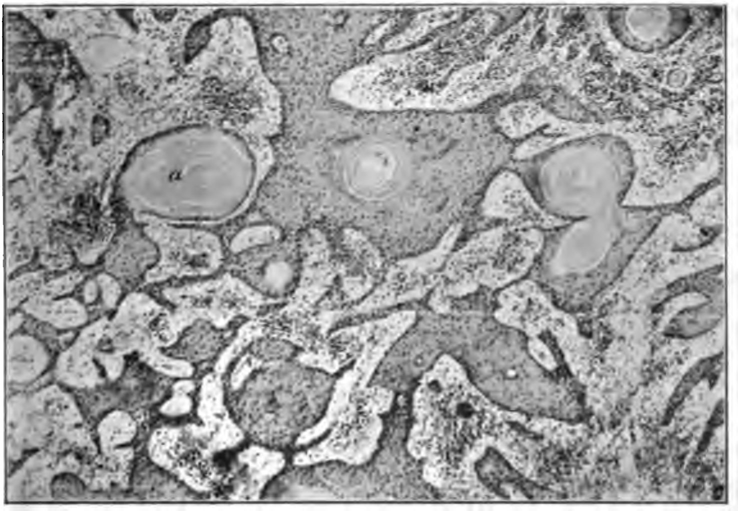
[1] On the distribution of rodent ulcer, see G. L. Cheatle, *Brit. Med. Journ.*, 1903 and 1904.

PLATE V.



A. Squamous-celled carcinoma of skin, showing infiltration of the epithelial cells. (Hæmatoxylin and eosin, × 30.)



B. Squamous-celled carcinoma of the scrotum, showing the cell-nests, *a*. (Hæmatoxylin and eosin, × 50.)

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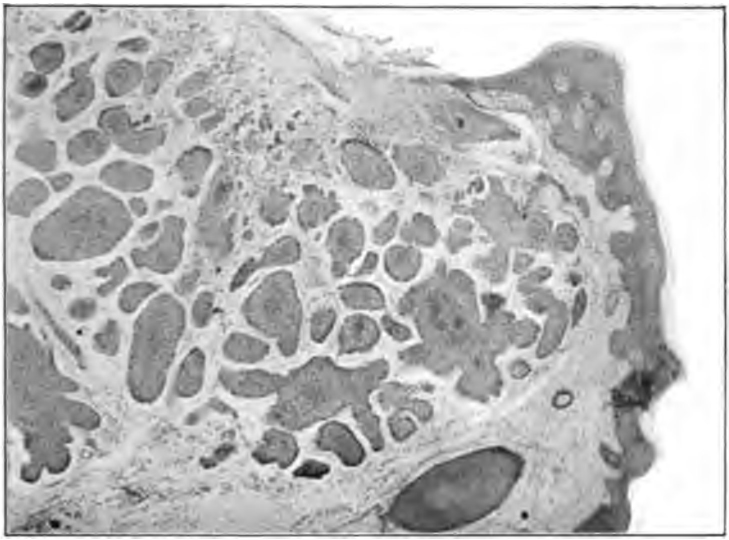
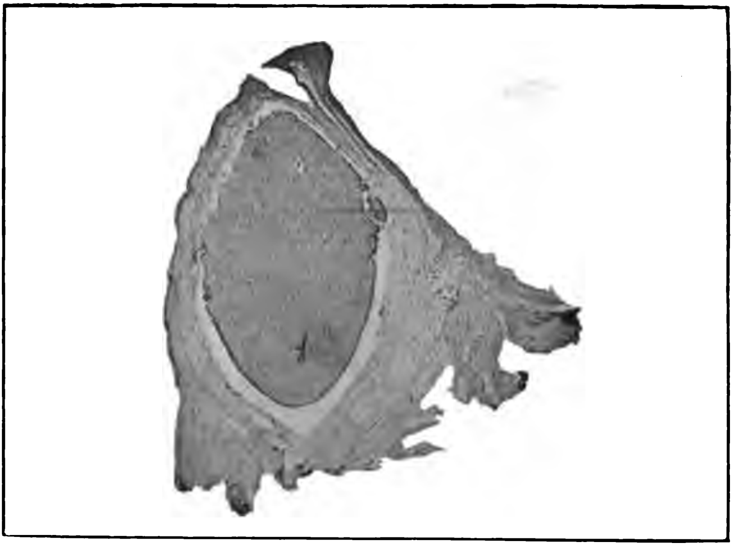
PLATE VI.



A. Rodent ulcer. (Hæmatoxylin and orange-rubin, × 40.)



B. A very young rodent ulcer developing in the region of a hair-follicle. (Hæmatoxylin and orange-rubin, × 10.)

To face page 58.

This neoplasm, having as it has such special characters, has been supposed to arise, not from the cutaneous epithelium, but from that of the hair-follicles, or possibly of the sebaceous glands (Plate VI., B.).

COLUMNAR-CELLED CARCINOMA.—In this variety the epithelium is of the columnar type. It is chiefly met with in the digestive tract from the pylorus to the termination of the rectum, less frequently in the stomach, in the ducts of acinous glands such as the mamma, in the bile-ducts, uterus, and occasionally in the respiratory tract. In the mamma this form of carcinoma is known as "duct cancer."

The tumours may be of large size, and in the intestine the growth generally involves the whole circumference, producing stenosis. Microscopically, the neoplasm consists of numbers of alveoli or tubes, irregular in size and shape, and lined with a single layer of columnar-celled epithelium, quite regular or in places showing a tendency to proliferate. Except for the fact that the alveoli invade and destroy the muscular layer and are irregular in shape, there is little to distinguish the columnar-celled carcinoma (microscopically) from a simple adenoma or hyperplasia.

The stroma consists of a delicate connective tissue, scanty in amount, and fairly cellular. In some instances the epithelial wall projects in the form of processes or papillomatous prolongations. This may produce a "villous carcinoma," or, if the lumen of the alveolus be dilated and the processes project into it, a "papillomatous or proliferating cyst-adenoma" results.

In the "duct cancer" of the breast the same features are seen in a minor degree, and small cysts containing the intra-cystic papillomata are present.

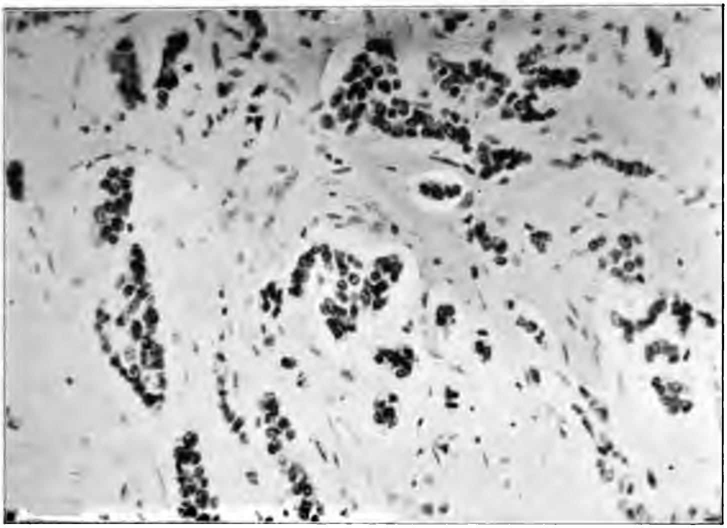
SPHEROIDAL-CELLED CARCINOMA.—This originates from the glandular epithelium of such organs as the mamma,

B. Scirrhous carcinoma of breast. (Same as A, × 240.)

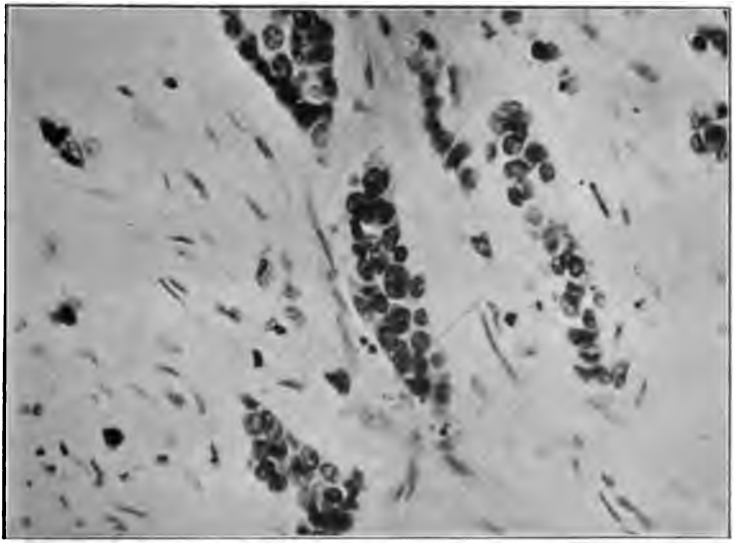
To face page 60.

pancreas, thyroid, salivary glands, kidney, prostate, testicles, and ovary, also in the stomach. Like the typical epithelium of a secreting gland, the cells are spheroidal, cubical, or polygonal, and the glandular structure may be reproduced to such an extent that the term *adeno-carcinoma* is frequently applied to this variety. But the cells depart from the glandular type in that the secretion proper to the gland is generally in abeyance, and the alveoli containing them are atypical and irregular in shape and arrangement. In a mammary carcinoma, a type of this variety, alveoli of all shapes and sizes are present, having no regular arrangement and packed with a variable number of cells of a spheroidal or polygonal shape, having well-defined, large, deeply-staining nuclei and a moderate amount of cytoplasm; no intercellular substance can be made out. Between the alveoli is a variable amount of fibrous tissue, plentiful and dense in the central, older, portions of the growth, more scanty, more delicate, and more cellular in the peripheral, younger, portions. If the fibrous tissue is abundant, the tumour is hard and of slower growth and is termed a *scirrhous carcinoma* or simply *scirrhus* (Plate VII., A. and B.); if the cells are in excess, the term *encephaloid* is sometimes applied. In some of the cases of spheroidal-celled carcinoma extensive colloid degeneration takes place, and the alveolus becomes more or less filled with the colloid material—*colloid cancer* (Plate XV., B.). In this the epithelial cells in the more central portions of the growth may be almost wanting, while at the periphery the structure is of the ordinary spheroidal-celled type, a series of transitional forms between the two being present. Colloid cancer is particularly met with in connexion with the digestive tract and the mamma. The secondary growths frequently show the colloid change.

PLATE VII.



A. Scirrhous carcinoma of the breast. (Hæmatoxylin and Van Gieson, × 125.)



B. Scirrhous carcinoma of breast. (Same as A, × 240.)

To face page 60.

Placentoma (deciduoma, or syncytioma malignum, chorion epithelioma) is described at page 462. It is probably derived from the epithelium of the chorionic villi, and is therefore an epithelial tumour or carcinoma.

Cystoma.—A cystoma must be distinguished from a cyst (see p. 39). It is a pathological new formation arising from active proliferation of a matrix and enclosing cystic spaces, and is generally multilocular, a simple cyst being unilocular. All the cystomata are practically adenomata with cystic spaces, *e. g.* the cystadenoma so often seen in the ovary (see p. 466 and Plate XXIII., B.) and the fibro-adenoma of the breast (see p. 469 and Plate XXIV., B.). Occasionally they may be malignant.

Teratomata are neoplasms which contain a varied assortment of tissue elements, mostly advanced so far developmentally as plainly to resemble one or more of the fully-developed tissues of the mature organism. In one kind of teratoma—the *dermoid*—structures appertaining to the skin are present, *e. g.* skin, hair, nails, and teeth; in others (to which the term "dermoid" should not be applied) the structures may be still more complicated—bone, muscle, nerve, parts of organs and viscera, and even recognisable fetal parts.

The nature of dermoid cysts has recently been the subject of a paper by Shattock.[1] He points out that the ordinary dermoid cyst of the trunk is sufficiently explained as due to epiblastic sequestration occurring during the closure of embryonic clefts. The cysts of the ovary and testicle, containing as they often do such highly differentiated structures as teeth and bone, are marked off from all others. Dentigerous cysts have been described in the neck, but for these a satisfactory explanation has been offered in viewing them as the results of an abortive anterior dichotomy. In a similar way, by an abortive posterior dichotomy, the presence of a third compound lower limb and certain of the sacral teratomata can be explained.

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[1] *Brit. Med. Journ.*, 1904, vol. ii, p. 1248.

The dermoid of the ovary has been explained as derived from the Wolffian duct, which is of epiblastic origin. Shattock, however, considers that the so-called ovarian dermoid is (with perhaps few exceptions) a teratomatous cyst, and should be known by this name, for it is not a cyst of the skin, but a smooth-walled cyst into which a skin-covered teratoma projects. Its formation has been ascribed to an abortive impregnation, which may be the case in some instances, but since it occurs in children such an explanation is not adequate, and cannot be applied to testicular dermoids. Shattock's theory is one of "epigenesis," viz. that the ovarian teratomatous cyst results from the fertilisation of the primordial ova in the embryo, so that the embryo furnishes a second imperfect individual, the origin of which is not, therefore, synchronous with, but later than, itself. In the lower animals "fertilisation" of the ovum may take place by methods other than the ordinary, *e.g.* by "shock," parthenogenesis, etc. As to the occurrence of teratomatous cysts of the testicle, the assumption is made that the organ had, in the embryo, contained primordial ova—that is, that the gland was an ovo-testis. Examples of this condition have been described by different observers in man.

THE ÆTIOLOGY OF NEOPLASMS.

No subject in pathology has been more discussed than the ætiology of neoplasms; and in spite of the large amount of theorising and research devoted to it we are still in the position of knowing very little concerning the causation of new growths in general. It is with the ætiology of carcinoma that most research has been done.

Neoplasms, non-malignant and malignant, are met with in all classes of vertebrates, if not of invertebrates, and in all races of man. The malignant neoplasms seem to be more frequent in civilised races and domesticated animals than in uncivilised races and wild animals. There is a general impression that cancer is on the increase in England and other countries, but there are no reliable statistics which prove this.

Virchow first propounded a theory of *mechanical irritation* as the causative factor of new growths. It is undoubtedly a predisposing factor in the causation of malignant growths—*e. g.* carcinoma of the lip frequently develops subsequent to the irritation of a clay pipe or ragged tooth, but cannot be held to be the *causa vera,* since the majority of new growths do not develop in situations liable to most irritation, nor does it explain the development of most non-malignant growths.

The *embryonic hypothesis* of Cohnheim refers the genesis of neoplasms to latent embryonic rudiments. Cohnheim believed that during development certain groups of cells, instead of developing normally into their proper tissues, become cut off from the neighbouring cells, and for a time remain dormant and inactive. Then, in consequence of some stimulus, *e. g.* alteration in the supply of nutriment or surroundings, irritation, etc., they begin to multiply and form a new growth. This theory accounts for the formation of many neoplasms, such as congenital ones, some of the teratomata, the growths arising in the kidney from adrenal rests, and the like. Virchow has even discovered islands of cartilage remaining unossified in bone which later might become the starting-point of chondromata.

There is, however, little histological evidence of the development of most neoplasms from embryonic residues. While this theory would explain the development of neoplasms, it is impossible to prove or disprove it, and it leaves unsolved the reason for the embryonic residue lying latent for long periods and then suddenly starting into activity. Beard has supported this theory in a modified form in a number of papers in the *Lancet* during the last two or three years, and although we have little proof or disproof of its correctness, there is perhaps a growing tendency to accept it.

Thiersch propounded a *lost balance* theory, which suggests that in carcinoma, for instance, there is a loss of balance between the epithelial and connective tissues, owing to degenerative changes in the latter, and resulting in an invasion by the former. It presupposes that the sub-epithelial tissues undergo retrogression, while the epithelium maintains its vigour, or, it may be, acquires special vigour.[1]

It is to be noted that normally something controls cell-proliferation. In uterine life cell-proliferation proceeds at an enormous rate, and in post-embryonic life cell-proliferation is continually going on for the purpose of repair. What controls the proper and regular cell-proliferation, and keeps this within the proper bounds? Is it some internal secretion, as might be suggested by the influence of the pituitary body on growth? At present we have no answers to these questions.

Adami[2] has propounded a theory which he terms the *habit of growth* of cells. From certain facts and arguments he arrives at the conclusion that "active cell-division and cell-proliferation occur only in conditions in which the cell cannot fully utilise the assimilated material (and the energy stored up in the assimilation of that material) in the performance of its specific functions.

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[1] See Morris, "Bradshaw Lecture on Cancer," *Brit. Med. Journ.* 1903, vol. ii, p. 1505, for summary of theories.

[2] *Brit. Med. Journ.*, 1901, vol. i, p. 621.

"Such conditions are to be met with where the tensions acting on the cell are reduced, and certain energies which before were necessary to counteract opposing forces are freed, and thus become capable of diversion from their purpose, or, again, where stimulation from without results in increased assimilation and storage of nuclear and cell material, which now from any condition cannot be utilised in the performance of specific function.

"In either case the cells will continue to proliferate so long as the primary modification of physical relationships or the primary stimulus continues to act, so long as there is adequate nutriment, and so long as the tensions exerted upon the cells do not become excessive.

"Provided that these conditions are observed, the greater the amount of cell proliferation, the greater the tendency for certain at least of the newly-formed cells to be projected from the relations proper to cells of the tissue giving them origin, the less will be the opportunity for such cells to carry on their primordial function, the greater the liability to proliferation.

"The longer the cells are diverted from their proper extrinsic functions to proliferative activity, the greater the momentum acquired by them to continue performing the proliferative act until the functional activities become largely suspended, and the "habit of growth" is set up.

"When this habit of growth is inaugurated, the cells can continue to grow and multiply in the complete absence of those conditions which initiated their proliferation in the first place, and we obtain that purposeless, functionless, cell-growth characteristic of the true tumour."

Parasitic theories.—The manner in which carcinoma and sarcoma produce metastases or secondary growths in distant parts, and the superficial resemblance which these neoplasms bear to some of the infective granulomata, naturally suggested that they might be caused by micro-parasites, and an immense amount of research has been devoted to attempts to isolate these supposed micro-organisms, chiefly from carcinoma. First, bacteria were suggested, and various bacilli were isolated, all proving on critical examination to be unassociated with the disease process.[1] Next, Russell described bodies which he regarded as fungoid in nature. Then, Ruffer and Plimmer and others described bodies in cancer cells (which are certainly present), round, single or multiple, apparently enclosed in a capsule, and possessing a nucleus (see Fig. 3, *a*), which they believed to be parasitic protozoa, probably sporozoa. These bodies (the Ruffer's or Plimmer's bodies) are plentiful in the growing edge and in rapidly growing carcinomata, and are absent from morbid tissues other than carcinoma and from normal

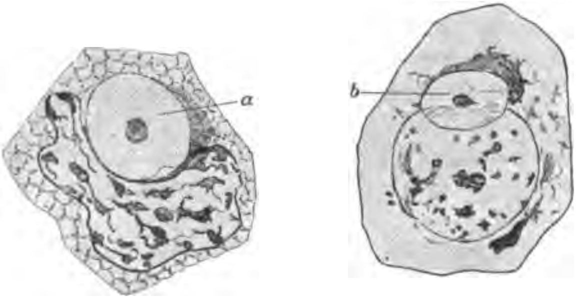

Fig. 3.—*a*, Ruffer's or Plimmer's body in a cancer cell; *b*, the archoplastic vesicle in spermatid of mouse (after Farmer, Moore, and Walker).

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[1] Doyen has recently described a micrococcus in carcinoma.

tissues. Moreover, undoubted protozoa, such as the *coccidium* of rabbit coccidiosis, are able to produce epithelial proliferation (though not carcinoma), which supported the idea that protozoa might cause the epithelial proliferation which is one of the essential features of carcinoma. All attempts to isolate a protozoon have failed, but this does not necessarily exclude the presence of such an organism, since it is extremely difficult to isolate and cultivate organisms of this class. Save for the presence of these structures, there is absolutely no proof that protozoa are present in, or are the cause of, carcinoma, and the protozoan hypothesis has not been substantiated. It is to be noted that the presence of these structures in carcinoma and in carcinoma only, and not in other tissues, normal or morbid, in no way proves their parasitic nature, since, carcinoma being a unique tissue, alterations or structures might well be present in it which are not met with elsewhere. Moreover, as recently shown, the Plimmer's bodies are indistinguishable from the archoplastic vesicles of *normal* reproductive cells (see Fig. 3, *b*). The significance of this fact is discussed below.

Subsequently, San Felice and others isolated yeast-like forms from malignant growths, and by inoculation apparently succeeded in producing malignant neoplasms. But critical examination has in all these cases shown that the growths produced are of the nature of granulomata and are not true malignant neoplasms.

From these and other facts the parasitic hypothesis of the origin of malignant neoplasms, particularly carcinoma, has during the last three or four years steadily been losing ground.

It is to be noted that the supposed analogy between an infective granuloma and a malignant neoplasm is a very false one. In the case of an infective granuloma, the parasitic organism, having been arrested at some point, causes the proliferation of cells of the tissue around it and the migration of cells from the blood, and so the mass of cells which forms the granuloma is produced. In the case of a carcinoma, cells detached from the primary growth, having been arrested, proceed to grow and multiply and constitute the secondary growths, the cells of the tissue around taking little part in their formation. Again, from inoculation experiments, the analogy between carcinoma and an infective granuloma breaks down. Carcinoma is inoculable only on an animal of the same species as that from which it was derived; it is very specific in this respect, and therefore human carcinoma is not inoculable on animals. In the case of carcinoma of mice, if a piece of the growth be inserted into a healthy mouse, the animal becomes cancerous, but the whole of the cancerous tissue within the inoculated animal is derived from the original piece of cancerous tissue transplanted; its own tissues do not undergo a cancerous metamorphosis. That is to say, the inoculation is a process of transplantation, not of infection.

Certain phenomena connected with the cytology of carcinoma which have recently been observed by Farmer, Moore, and Walker[1] must now be discussed. When a somatic or ordinary cell of an animal divides mitotically certain definite changes occur in the nucleus. The chromatin aggregates into delicate strands which segment into a number of rod or V-shaped bodies termed *chromosomes*. The number of chromosomes thus formed is always the same for the same species of animal, though varying in different species. Thus in man there are always thirty-two chromosomes in the dividing somatic cells. The chromosomes next arrange themselves in a definite manner on the equator of a spindle-shaped structure (Fig. 4), and every one then splits longitudinally into halves, which separate, each travelling to opposite poles, and furnish the material out of which the two daughter nuclei are constituted.

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[1] See *Nature*, vol. lxix, 1904, p. 319, and *Brit. Med. Journ.*, 1903, vol. ii, p. 1664; *Nature*, vol. lxxii, 1905, p. 164, and *Brit. Med. Journ.*, 1905, vol. i, p. 1277; *Lancet*, 1905, vol. ii, p. 352; *Path. Soc. Trans.*, vol. lv, 1904, p. 449.

This form of mitosis (somatic mitosis) occurs in the earliest divisions of the fertilised ovum, but as division proceeds a stage is reached at which certain cells become differentiated from their fellows by a different form of nuclear division, which is termed *heterotype* mitosis. This is characterised by the fact that the chromosomes are not so well marked, and exhibit a bunched appearance, and by cohesion in pairs appear in only half the number (viz. for man sixteen) present in the somatic mitosis; moreover, they divide *transversely* instead of longitudinally, and do not assume such marked V-shapes, being more in the form of rings and loops (Figs. 5 and 6). Subsequently the descendants

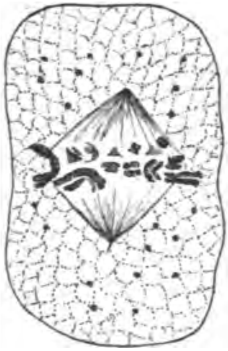

Fig. 4.—Chromosomes in somatic mitosis. Note V-form and longitudinal splitting (after Walker).

of the cells which have divided by heterotype mitosis retain the reduced number of chromosomes, but otherwise conform to the normal somatic mitosis. To the post-heterotype mitosis the term *homotype mitosis* or reduction division is applied. The cells which thus become differentiated and show reduction division are

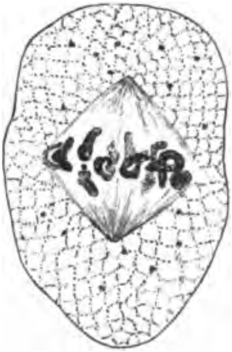

Fig. 5.—Chromosomes in heterotype mitosis. Note their thickness and irregularity, and the transverse division in one of them (after Walker).

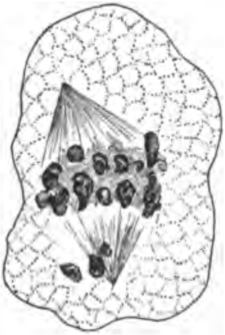

Fig. 6.– Heterotype mitosis from human testis (after Walker).

the sexual or reproductive cells, and the tissue in which they are present may be termed *gametogenic.*

Now, in the growing margin of a carcinoma it is found that many of the cells *show reduction division*—*i. e.* there is a transformation into cells in this respect resembling the reproductive or sexual cells, and from its likeness to the gametogenic such tissue may be termed *gametoid* (Fig. 7). Other irregularities in the cells of the neoplasm also occur. It is of considerable interest that this reduction division and gametoid tissue seem to *occur only in malignant neoplasms.*

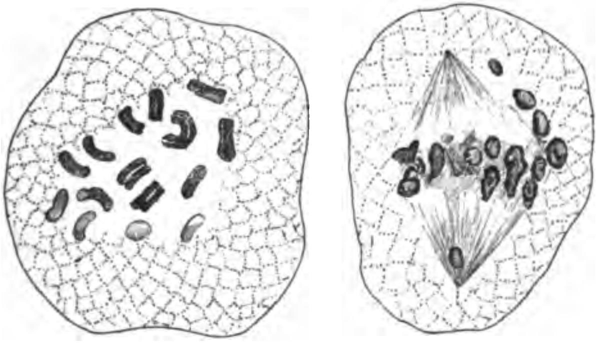

Fig. 7.—*a*, Homotype division in epithelioma (polar view); *b*, heterotype aster in epithelioma (after Walker).

Another remarkable fact recently demonstrated by Farmer, Moore, and Walker is that in the normal reproductive tissues structures occur which are strikingly similar to the bodies ("cancer bodies") described by Ruffer, Plimmer, and others in cancerous growths, and regarded by many as parasites. These structures in the reproductive tissues are the archoplastic vesicles, and that similar structures should occur in cancerous growths (and not, be it noted, in benign tumours) on the one hand lends additional support to the idea of the gametoid nature of the cancer cells, and, on the other hand, further disproves the supposed parasitic nature of the "cancer bodies." Is it possible from these observations to formulate a suggestion as to the nature of the cancer process?[1] Professor Farmer himself has stated that he and his co-workers do not profess to explain the relation between the homotype mitosis of the gametoid cells of cancer and the life-history of cancer. It might be that the gametoid cells of the malignant growth undergo some process of fertilisation giving rise to an aberrant embryo, as it were, which by development forms the primary growth, and which would thus be parasitic on the host, the secondary growths arising from a repetition of the primary event. In some plants gametogenic tissue may normally possess parasitic characteristics. There is, however, so far little evidence of fertilisation or fusion of the gametoid cells in cancer, but Farmer, Moore, and Walker[2] have observed included leucocytes within the cancer cells, not apparently simply engulfed phagocytically, but undergoing division, and their chromosomes undergoing mixture or fusion with the chromosomes of the cells. Farmer, Moore, and Walker suggest that it is possible that the malignant elements are the outcome of a phylogenetic reversion, but this would not necessarily explain the *invasiveness* of cancer. In spite of recent work much remains to be done and to be explained before we shall be in a position clearly to understand the cancer process.

With regard to the causes which lead to the production of the gametoid cells in cancer, it has been found that in plants various stimuli will rapidly bring about heterotype mitosis, and, given the proper stimulus, probably any somatic cell may become changed into this type. The connexion between chronic irritation and cancer has long been recognised, though the manner in which this factor acts to produce cancer has not been understood, but in the light of the foregoing it may be regarded as one of the stimuli which may bring about heterotype mitosis and reduction division.

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[1] See Hewlett, *Nature*, vol. lxxii, 1905, p. 295.

[2] *Lancet*, 1905, vol. ii, p. 352.

Professor B. Moore has shown that the development of carcinoma is associated with a diminution of the gastric hydrochloric acid, no matter where the malignant growth is situated (p. 324). A recent investigation by B. Moore, Roaf, and Whitley[1] has shown that the diminution in the secretion of hydrochloric acid is due to a change in the distribution of salts in the plasma, whereby the alkalinity is increased. It was also found that the addition of small amounts of alkalies to the sea-water in which the fertilised eggs of *echinus* (sea-urchin) were developing caused an increased rate of growth and division, together with atypical forms of mitosis, which closely resembled the pathological divisions seen in the growths of malignant disease.

[1] Royal Society, November 23rd, 1905.

CHAPTER IV.

INFLAMMATION.

INFLAMMATION.[1]

WHEN a living tissue is injured or damaged, a series of complex local changes ensues, tending generally to repair, and these are comprised under the term "inflammation."

It is difficult or impossible to give a concise definition of inflammation. One of the best, which is repeatedly quoted, is that of Burdon Sanderson: "*The process of inflammation is the succession of changes which occurs in a living tissue when it is injured, provided that the injury is not of such a degree as at once to destroy the structure and vitality of the tissue.*" Adami objects that this definition includes too much, *e. g.* the hæmorrhage, or subsequent atrophy, and suggests the following: "*Inflammation is the series of changes constituting the local manifestation of the attempt at repair of actual or referred injury to a part, or, briefly, as the local attempt at repair of actual or referred injury.*" This definition has the objection that it seems to imply a *purposive* action to the tissues which cannot be admitted; the phrase "referred injury" has been introduced because hypnotic suggestion appears to produce some of the phenomena of inflammation. Sidney Martin's definition is perhaps as good as any: "*Inflammation may be considered as a reaction of the tissues to the irritant effect of an injury, mechanical, chemical, thermal, or bacterial.*"[1]

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[1] See Adami, in Clifford Allbutt's *System of Medicine*, vol. i.

From the time of Celsus (first century A.D.) four cardinal signs and symptoms of inflammation have been recognised—redness (*rubor*), swelling (*tumor*), heat (*calor*), and pain (*dolor*), to which a fifth was later added, viz. the disturbance, impairment, or arrest of function (*functio læsa*) in the injured part. None of these is, however, characteristic or a necessary part of inflammation, one or other frequently being absent.

Reaction to injury is a common feature exhibited throughout the animal kingdom, and it may be well first briefly to describe the events which follow the infliction of an injury in the lower animals. Among the protozoa, which are unicellular organisms, much depends on the presence and integrity of the nucleus. If an amœba be divided into unequal portions, one containing the nucleus, the other not, the latter dies, while in the former the injured region, by a process of closure and growth, rapidly becomes regenerated. If a foreign particle be ingested, a food vacuole forms around it, an acid digestive fluid is secreted, and the particle is digested, if this be possible, or if not, it is soon extruded. In the lower metazoa, with an incomplete vascular system, the leucocytes always collect in the injured region. Thus, as was shown by Metchnikoff, if a *daphnia* (the water flea) be infected with the spores of a yeast-like organism (*monospora*), the leucocytes quickly gather round each spore, forming a mass of plasmodium, and eventually digest and destroy it. In a non-vascular area in a lower vertebrate, *e. g.* the embryonic axolotl, a fish-like amphibian of American lakes, the leucocytes (wandering cells of the tissues) similarly collect in the injured area.

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[1] *Manual of General Pathology*, p. 1.

In the higher vertebrates it is necessary to consider the events which follow an injury, both in an avascular and in a vascular tissue. The cornea is convenient for many reasons in which to study the effects of injury in an avascular tissue; it consists of layers of fibres enclosing lymph-spaces in which lie the corneal corpuscles or cells, and there are no blood-vessels. If a small lesion, without solution of continuity, be produced by touching a spot in the centre of the cornea with chloride of zinc, it will be found that (1) a certain number of the corneal corpuscles will be destroyed as the direct result of the injury, and (2) in a zone surrounding this the corneal corpuscles are enlarged and tumefied. There is no collection of leucocytes, and the corneal cells multiply and replace those which have been destroyed. If, however, in addition to the damage produced by the caustic, a minute lesion of continuity be made, it will be found that a small opacity soon forms, due to the collection at the site of injury of numbers of round cells. These, from their characters, are leucocytes, and there is no evidence of the proliferation of the corneal corpuscles. There is, at the same time, no evidence of any alteration of the vessels at the periphery, and it may therefore be legitimately assumed that these leucocytes are those which are present in the cornea itself.

If the injury be of greater intensity, and particularly if some of a culture of the *Micrococcus pyogenes aureus* be injected into the cornea, *i. e.* if a *septic* injury be produced, it will be found that the micrococci multiply and spread along the lymph-spaces from the seat of inoculation, forming a branching mass, and around this a zone of degenerate corneal corpuscles is present. After twenty-four hours have elapsed numbers of leucocytes will be found to have collected around this area, and are seen converging towards it along the lymph-spaces. At the same time, the vessels at the periphery of the cornea appear enlarged and congested, and it is evident that leucocytes are passing out of the vessels into the neighbouring tissue spaces, from whence they make their way centrally towards the seat of injury. So much for the phenomena which follow various degrees of injury in the cornea, the type of an avascular tissue.

In a vascular tissue the reaction following an injury is more complicated, and may, again, be considered to be of three degrees: (1) a simple non-irritative injury, (2) a more severe irritative injury, and (3) a septic injury.

If a small incision be made with a sharp, clean, aseptic knife through the skin and subcutaneous tissue, the reaction is of the slightest, repair rapidly ensues if the divided tissues be brought into apposition, and *primary union*, or *union by first intention*, is the result. The cut divides a few capillary vessels, which, however, immediately collapse and become occluded, so that the hæmorrhage is of the slightest. Soon after the infliction of the injury a slight exudation occurs, which glues together the surfaces of the incision, by coagulation and the formation of fibrin. A few leucocytes invade this coagulum and the neighbouring region of injury; a certain number of epithelial and connective-tissue cells will have been destroyed and damaged by the incision and show more or less degeneration, and this is practically all the evidence there is of the effects of the injury. Soon, within forty to forty-eight hours, the cells in the neighbourhood become enlarged, multiply, and send out processes into the fibrinous coagulum, which thus becomes an organised cicatrix, capillary vessels at the same time developing from those around, and thus a vascular tissue is once more reproduced.

It will be seen, therefore, that both in a non-vascular and in a vascular tissue, a slight non-irritative injury is followed by reaction of the smallest, and mainly confined to the cells of the part.

The events, however, which follow injuries of the second degree are those of the greatest interest. Such an injury may be studied in the web of the frog's foot by applying a particle of mustard, or snipping out a tiny wedge of skin, or by applying diluted croton oil to the tongue of a frog, or exposing the mesentery to the air, etc. The course of events which follows such an injury cannot be better described than in the words of Cohnheim :[1]

"The first thing you notice in the exposed vessels is a dilatation, which occurs chiefly in the arteries, then in the veins, and least of all in the capillaries. With the dilatation, which is gradually developed, but which during the space of fifteen to twenty minutes has usually attained [illegible]nsiderable proportions (often exceeding twice the [illegible]ginal diameter), there immediately sets in in the mesen[illegible]ry an acceleration of the blood-stream, most striking again in the arteries, but very apparent in the veins and capillaries also. Yet this acceleration never lasts long ; after half an hour or an hour, or sometimes after a shorter or longer interval, it invariably gives place to a decided retardation, the velocity of the stream falling more or less below the normal standard, and so continuing as long as the vessels occupy their exposed situation. Such is the course of events in the mesentery experiment, in which not only the vessels of the mesentery but their terminal ramifications in the intestine are laid bare. In the wound of the tongue, on the other hand, the acceleration is often altogether absent, and from the first there is associated with the dilatation a retardation of the stream, which increases as the dilatation increases. This is the case, at least, when a number of larger branches are exposed in the wound, but not in their finer ramifications. Should the latter also be laid bare a temporary acceleration precedes the slowing of the blood-stream, which never fails finally to set in in the exposed vessels.

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[1] *Lectures on General Pathology*, vol. i, p. 248 (New Sydenham Society's translation, 1889).

"This stage having been reached, the vessels are seen to be all of them very wide; a multitude of capillaries which were formerly hardly perceptible can now be clearly distinguished; pulsation is unusually conspicuous on into the finest ramifications of the arteries, while the flow is everywhere slower than normal, so that the individual corpuscles may easily be recognised, not only in the capillaries but also in the veins, and during diastole even in the arteries. In consequence of the tardy forward movement the corpuscles accumulate in large numbers in the capillaries, so that the latter appear redder than usual, and therefore fuller, more voluminous; yet their cross-section, as just stated, is only very inconsiderably enlarged. But it is the veins rather than the capillaries that attract the notice of the observer, for slowly and gradually there is developed in them an extremely characteristic condition; the originally plasmatic zone becomes filled with innumerable colourless corpuscles. The plasmatic zone of the veins, you will remember, is always occupied by scattered colourless blood-corpuscles, which, owing to their globular form and low specific gravity, are driven into the periphery of the stream, and whose adhesiveness makes it difficult for them to escape from the wall once they have come into contact with it. It is obvious that this difficulty will be enhanced in proportion to the slowness of the blood-stream, and thus it is not surprising that a gradual accumulation of large numbers of colourless corpuscles should take place in the peripheral zone and here come to be comparatively motionless. For that a state of absolute rest—an actual standstill—is out of the question I need hardly mention expressly; the colourless cells of the plasmatic layer remain stationary at most for a time; they then advance a little, and perhaps make another short halt, and so on. Yet this does not lessen the striking contrast presented by the central column of red blood-corpuscles flowing on in an uninterrupted stream of uniform velocity, and the peripheral layer of resting colourless cells. The internal surface of the vein appears paved with a single, but unbroken, layer of colourless corpuscles, without the interposition at any time of a single red one. It is the separation of the white from the red corpuscles that gives the venous stream in these cases that characteristic appearance, anything analogous to which you will look for in vain in the other vessels. For in the capillaries, although large numbers of colourless blood-corpuscles adhere to the walls, there is always an admixture of red cells, or rather, these are very decidedly in the majority. Lastly, in the arteries there is seen during diastole, almost at the moment of exit of the wave, a number of colourless blood-corpuscles rolling straight towards the periphery; yet these are always swept into the stream at the next systole, so that the development of a resting peripheral layer is here altogether out of the question.

"But the eye of the observer hardly has time to catch all the details of the picture before it is fettered by a very unexpected occurrence. Usually it is a vein with the typical peripheral arrangement of the white corpuscles, but sometimes a capillary, that first displays the phenomenon. A pointed projection is seen on the external contour of the vessel-wall; it pushes itself further outwards, increases in thickness, and the pointed projection is transformed into a colourless rounded hump; this grows longer and thicker, throws out fresh points, and gradually withdraws itself from the vessel-wall, with which at last it is connected only by a long thin pedicle. Finally, this also detaches itself, and now there lies outside the vessel a colourless, faintly glittering, contractile corpuscle, with a few short processes and one long one, of the size of a white blood-cell, and having one or more nuclei—in a word, a colourless blood-corpuscle. While this is taking place at one spot, the same process has been carried on in other portions of the veins and capillaries. Quite a large number of white blood-cells have betaken themselves to the exterior of the vessels, and these are constantly followed by fresh ones, whose place in the peripheral layer is immediately occupied by others. Like every stage of the entire process on from the moment of exposure, these phenomena may develop either rapidly or slowly. At one time the earliest emigration very quickly succeeds the pavementing; at another an hour or more may pass without anything happening to draw attention to the contour of a single vein or capillary. In any case the final result, after six or eight or more hours have elapsed, will be the enclosure of all the veins, small and large, of the mesentery or wound of the tongue with several layers of colourless blood-corpuscles. These fence in the veins, in the interior of which the previously described conditions continue, namely the peripheral arrangement of the colourless cells and the central unbroken flow of red blood-corpuscles. Nothing analogous has occurred in connexion with the arteries; their contour has remained smooth as before, nor can a solitary corpuscle, red or white, be discovered on their outer surfaces, except, of course, such as may have reached them from the neighbouring veins. On the other hand, the capillaries take, as already mentioned, a very active part in the process, yet these and the capillary veins differ remarkably from the veins proper in that not merely colourless but red corpuscles emigrate from them. This result is completely in harmony with the condition of the stream in these vessels, for I have already called your attention to the fact that in the veins white corpuscles only, in the capillaries both varieties, are in contact with the vessel wall, so that whether a preponderance of white or of red corpuscles passes out of a given capillary depends solely on the numerical relations of the cells accumulated in its interior. Keeping pace with this exodus, emigration, or, as it is also called, extravasation of corpuscular elements there occurs an increased transudation of fluid, in consequence of which the meshes of the mesentery, or the tissues of the tongue, are infiltrated and swell. But this is not all. The extravasated colourless corpuscles distribute themselves, in proportion as their numbers increase, over a larger area, forsaking the neighbourhood of the vessels from which they were derived. The tissues become more and more densely packed with them, while the red cells, which have not the power of independent locomotion, remain located in the vicinity of their capillaries, yet these also may be carried off by the stream of transudation. Soon a moment must arrive when the products of exudation and transudation can no longer be accommodated in the tissues. They now gain the free surface of the mesentery, and should the transuded fluid coagulate, as is the rule here, the final result of the processes just described will be the deposition on the mesentery, as well as on the intestine, of a fibrinous pseudo-membrane, densely packed with colourless blood-corpuscles, and interspersed with isolated red cells."

Such is Cohnheim's graphic description of an injury in a vascular area. The events may be summarised as follows:

(1) *Dilatation*, first of the arteries, then of the veins, and lastly of the capillaries (this is sometimes preceded by a brief *constriction* of the arteries at the moment of the infliction of the injury).

(2) *Acceleration of the blood-stream.*

(3) *Retardation of the blood-stream*, with *pavementing of the leucocytes* in the plasmatic zone.

(4) *Stasis.*

(5) *Emigration of leucocytes* (so-called margination), *diapedesis of red corpuscles*, with *exudation of serum.*

The subsequent changes, provided the irritant act no further, are in the direction of resolution and repair. The circulation gradually becomes re-established, the exudation becomes absorbed, the epithelial cells (if a piece of the skin has been removed) around the injury proliferate, and the leucocytes disappear, so that after twenty-four hours or so the tissue has returned to the normal. If, however, the irritant continues to act, and particularly if sepsis (infection with micro-organisms) occurs, the process may terminate in *suppuration.*

Emigration of leucocytes continues, the vessels at the centre of the area become plugged with leucocytic thrombi, the tissues disintegrate and dissolve, partly as a result of the action of enzymes secreted by the micro-organisms and partly through the action of enzymes liberated through the tissue and cellular disintegration, and a space or abscess results filled with pus, which consists of leucocytes, principally of the polymorphonuclear variety, the pus-cells, floating in a serous fluid, the pus-serum. It will thus be seen that in the lower animals the wandering cells play an important *rôle* in reaction to injury, and that in the higher animals the accumulation of leucocytes and wandering cells in the injured area is equally constant, and perhaps the most striking feature of the reaction to injury. The various factors of the inflammatory process may now be considered more in detail.

The blood and blood-vessels in inflammation.—The transitory constriction of the arterioles, which may be the first result of the action of the irritant, is probably a direct and not a reactive one, and due to stimulation of the vaso-constrictor nerve-endings, or of the muscle itself. The dilatation which rapidly follows must be regarded as reactive, and is due either to a direct action of the irritant on the muscle of the vessel-walls or on the nerve-endings. That it is not reflex or due to vaso-motor paralysis is shown by the fact that a further dilatation ensues if inflammation be produced in a vascular area in which the vessels are already dilated after section of all the nerves going to the part.

The next event noticed, the *accelerated circulation*, is generally stated to be a direct result of the dilatation and increase in the amount of blood, but unless the latter be considerable, on physical grounds dilatation should be associated with slowing. Acceleration is, however, seen in paralytic dilatation, *e. g.* in the frog's web when the spinal cord is destroyed, and it may be of the nature of an active hyperæmia, an increased determination of blood to the part.

The subsequent *slowing of the circulation*, is probably the result of several factors—increased resistance, due to massing of the corpuscular elements in the small veins and capillaries; increased viscosity of the blood, owing to transudation of fluid out of the vessels into the surrounding tissues; and particularly changes in the vessel walls, causing increased frictional resistance to the flow of blood. As regards the last-named it is found that if milk be substituted for the blood the fat globules are impeded in their flow through an inflamed area, just as the corpuscles are. It is not unlikely that the endothelium becomes more adhesive, so that the corpuscles, especially the leucocytes, have a tendency to stick to the vessel walls.

The marked reaction of the blood-vessels which occurs in inflammation led Cohnheim to regard an alteration in the vessels as being the basis of inflammation. The alterations in the vessels seem to be of such a nature as to render their walls more permeable, but whether they are simply passive and caused by the irritant, or whether they are active and due to contraction of the endothelial cells is uncertain. The endothelial cells are contractile, and frequently enlarge and project into the lumina of the vessels, tending to increase the resistance to the flow of blood, and in many instances they may be seen to have proliferated.

The *altered distribution* of the corpuscular elements is entirely explicable on physical grounds. This has been demonstrated by Hamilton[1] in a number of ingenious experiments which do not seem to have received the attention they merit. By passing spheres and discs of spermaceti, paraffin, and gelatin of various specific gravities suspended in water and other fluids at different rates through tubes of various sizes he showed that—

(1) The difference in position of the coloured and colourless corpuscles circulating in a vessel is not owing simply to the one being heavier than the other, but to

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[1] See *Text-Book of Pathology*, vol. i, p. 195.

the specific gravity of the coloured being nearly alike with the plasma, while that of the colourless is considerably less.

(2) The rotating motion of the colourless is due to their coming in contact with the wall of the vessel.

(3) The difference in their rapidity of motion is accounted for by their respective situations in the axial and peripheral streams.

(4) A certain rapidity in the flow of blood through the vessels is absolutely necessary to keep the colourless corpuscles circulating. Whenever this is diminished they tend to accumulate in the peripheral zone and to obstruct the onward passage of the coloured.

The *emigration of the leucocytes* was first observed by Waller (1846) and Addison (1849), and subsequently re-described by Cohnheim. In the early stages of inflammation there is usually a far greater tendency for the leucocytes to exude than for the chromocytes to do so. This seems to be owing to the fact that the leucocytes are applied in large numbers to the internal surface of the small veins, and must therefore be the first element to pass through the vessel wall. In rapidly occurring inflammations, *e. g.* pneumonia, and after the sudden ligature of a vein, in which instances there has been no time for the pavementing of the leucocytes, the chromocytes are found to exude in numbers equal to, or even greater than, the leucocytes. The emigration of the leucocytes must be regarded as an *active* process due to their inherent capacity of movement, aided also by increased intra-vascular pressure. The red corpuscles, on the other hand, are simply *pushed through* the vessel-walls (*diapedesis*) owing to the rise of intravascular pressure, the result of stasis. At one time it was supposed that there were actual apertures, or stomata, in the vessel walls through which the corpuscles passed; but this idea is now given up, and it is believed that the cement substance between the endothelial cells becomes loosened or softened, either as a result of nutritive changes or possibly through the action of enzymes.

The active emigration of the leucocytes is now regarded as being due to the attractive influence of certain chemical substances, or "*chemotaxis,*" as it is termed. It has been found that living cells, such as bacteria, infusoria, etc., are attracted by some substances and repelled by others, and it can be shown that a similar influence is exerted on leucocytes. If capillary tubes filled with croton oil, turpentine, or certain bacteria or bacterial products be inserted into the living tissues, leucocytes will migrate into the tubes; this is termed *positive chemotaxis.* If the tubes be filled with quinine, chloroform, dilute acids, and certain other bacteria and bacterial products, the leucocytes will be repelled; this is *negative chemotaxis.* Most inflammations attended with any great degree of leucocytic emigration are due to microbial agencies, or their products, which, as a rule, exert a positive chemotaxis; hence the collection of the leucocytes. The reason for this assemblage of leucocytes is for protective purposes; the leucocytes tend to ingest the bacteria, and so to bring to an end the cause of the inflammation. The leucocytes (and cells) having this power of ingesting bacteria were termed by Metchnikoff "*phagocytes,*" and the process of ingestion "*phagocytosis,*" and on these facts he based his well-known phagocytic theory of immunity (see p. 113).

The phagocytic cells are the large mononuclear and polymorphonuclear leucocytes, endothelial, and probably certain fixed connective-tissue, cells.

The *increased transudation* of fluid may be regarded as due to the increased intra-vascular pressure and to the alterations in the vessel-walls (*cf.* œdema). The amount is largely influenced by the *kind* of inflammation and its situation ; thus, in a dense tissue there is little exudation, while into a serous cavity it is considerable. The exudation may in some cases tend to cause resolution, for it must dilute the irritant and exert a "flushing out" action.

The *swelling* of the inflamed area is caused by the increased amount of the blood in the part and by the transudation of fluid into the tissues.

The *redness* of an inflamed part is due to the presence of a larger amount than normal of arterial blood.

The *increased temperature* is also due to the increase in the amount of blood and of the velocity of the circulation. The temperature of the inflamed part never exceeds that of the blood, though if there be fever it may be higher than normal.

The *pain* is generally stated to result from pressure by the exudation on the nerve-endings. This may be the case to some extent, and it is well recognised that there is often much more pain in a dense tissue, *e. g.* the periosteum or root of a tooth, in which the exudation is confined, than in an open tissue. But in œdema there may be enormous transudation and swelling, and therefore pressure in the tissues, without any pain. Probably a good deal of the pain is due to the irritant action of the irritant, or of the fluids transuded, on the nerve-endings. The pain is sometimes *referred* to a distant part, *e. g.* in pleurisy it is frequently felt in the abdomen.

Suppuration is simply the extension of the process of emigration of leucocytes.

The nervous system in inflammation.—The inflammatory process is undoubtedly modified by an intact nervous system, but inflammation will take place without the intervention of central nervous influences. It is impossible to exclude the action of local nerve-centres, such as ganglia, in experiments on inflammation, and the part these play in the inflammatory process is therefore uncertain. If the sympathetics (vaso-constrictors) be cut on one side, and the auricular branches (vaso-dilators) on the other side, in the neck of a rabbit, it will be found that inflammation of the ear on the cut sympathetic side is acute and of the type described, but progresses to recovery, while that on the cut auricular side is characterised by stasis without hyperæmia, and tends to necrosis. In persons susceptible, hypnotic suggestion that a burn has been caused on the skin will lead to hyperæmia, redness, exudation, and swelling at the spot, *i.e.* the changes of acute inflammation, showing that the nervous system may influence or even originate inflammatory changes.

The tissue-cells in inflammation.—The changes in the tissues in inflammation are partly retrogressive, partly progressive. The first action of the inflammatory agent, whatever its nature, is to produce damage and retrogressive changes—*e.g.* cloudy swelling, mucoid and fatty degeneration of cells, segmentation of muscle-fibres, and swelling and solution of connective-tissue fibres. If the agent continues to act, necrosis of the fixed cells of the connective tissue and of the leucocytes may result. But when the acute stage subsides, even if necrosis, ulceration, or suppuration has taken place, progressive or regenerative changes, tending to repair, ensue. These consist in the proliferation of the fixed connective-tissue and other cells of the part and the formation of young tissue known as *granulation tissue.*

Microscopically, granulation tissue consists of several different elements, together with capillary blood-vessels:

(1) cells which are clearly polymorphonuclear leucocytes, which apparently disappear and take no part in the formative process; (2) cells of varying size and shape, generally large and more or less spindle-shaped, with single oval nucleus and abundant cytoplasm. These are fibroblasts, and are in the main (if not entirely) derived from the fixed connective tissue cells; (3) cells indistinguishable from large mononuclear leucocytes. These in lower animals, *e.g.* the tadpole (Metchnikoff), seem also to help to form the fibroblasts, and may do so in man, but this is uncertain. Many pathologists hold that fibroblasts are derived only from connective-tissue cells; (4) multinuclear giant cells are not infrequent, particularly in certain chronic inflammations, *e.g.* tuberculosis. Their origin has been variously ascribed to fusion of leucocytes, epithelial, endothelial, and connective-tissue cells, or by division of the nucleus of the plasma cell, the cytoplasm remaining undivided, and they probably fulfil a phagocytic function; (5) small round cells, some of which are small lymphocytes, others plasma cells; (6) mast-cells. The plasma cell is common in many chronic inflammations, and was first observed by Waldeyer and subsequently studied by Unna.[1] It is described as a large, more or less rounded, or polygonal cell with strongly basophile and somewhat granular cytoplasm, and a nucleus, usually single, excentrically placed, staining a lighter tint than the cytoplasm, and containing one or two nucleoli. It can be differentiated by staining with Unna's polychrome methylene blue or better with Pappenheim's methyl-green pyronin. It has been variously derived from the lymphocytes and the connective-tissue cells, but Whitfield suggests that it is

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[1] "On the Plasma Cell," see Councilman, *Journ. of Exper. Med.*, vol. i, 1897; *Progressive Med.*, March, 1899, p. 247; and a good summary by Whitfield, *Brit. Journ. of Dermatology*, January and February, 1904.

produced locally from the endothelium of vessels and of the perivascular spaces. Mast-cells are large cells with cytoplasm containing numerous small basophile granules which stain purplish with methylene blue.

The healing of open wounds is accomplished by granulation; this is termed healing by secondary union or second intention. The fibroblasts proliferate, and formation of capillaries proceeds until the defect is made good. The walls of the capillaries become thicker, fibrillæ of fibrous tissue are developed, and a cicatrix is formed, its surface being covered by proliferation and extension of the neighbouring epithelium. A suppurating wound heals or an abscess cavity becomes filled up practically in the same manner, though the process may be delayed; and in a wound a coagulative exudation may cover the surface, become dry, and form a scab under which the granulation and formation of fibrous tissue proceeds—healing by scabbing.

Many variations occur during the healing process; this may become chronic and the amount of fibrous tissue be excessive, and by subsequent contraction considerable scarring and deformity result. Masses of necrotic tissue may be cast off or may become enclosed and encapsuled, etc.

CHAPTER V.

INFECTION—VEGETABLE AND ANIMAL PARASITES—IMMUNITY AND ANTI-BODIES—THE PRINCIPAL PARASITIC ORGANISMS AND THE DISEASES WHICH THEY PRODUCE.

INFECTION.

By the term INFECTION is meant the invasion of the living tissues by living micro-organisms which grow and multiply at the expense of the host. A disease produced by the growth and multiplication of micro-organisms is termed an *infective disease,* and is transmissible in most instances by inoculation. If the micro-organisms are from time to time discharged from the body of the host, either with the excreta, secretions, desquamated particles, or in some other way, the disease becomes *infectious* or *contagious* according to the ease with which another individual becomes *infected,* and the material which conveys the infection is often termed the *contagion.* Thus in scarlatina and smallpox the contagion is very readily conveyed from person to person even for a distance through the air, and these are infectious diseases. Ringworm and tuberculosis, as a rule, require more or less close contact for infection to take place, and these are therefore contagious diseases; while malaria is neither infectious nor contagious, since persons in the neighbourhood never directly contract the disease, though it can be conveyed by inoculation, and it is therefore infective only. But the distinction between *infectious* and *contagious* is mainly one of degree, and these terms have now to a large extent been given up. Excluding individual susceptibility, the relative infectivity of a disease probably depends on three factors: (1) The contagion gains access by the respiratory tract, (2) the contagion is freely given off aerially and is not destroyed thereby, and (3) the relative virulence of the contagion; in some instances the smallest amount of the contagion is sufficient to infect. If the contagion can gain access only through a wound or the digestive tract, the chances of infection may be largely reduced. In certain instances infection is conveyed by an intermediary, *e. g.* the mosquito in malaria, and in such cases infectivity will obviously depend on the presence and abundance of the intermediary. Infection is manifestly a part of the whole subject of parasitism, which includes the animal and vegetable parasites which develop in the animal body. If, however, the subject of parasitism is considered more closely, it will be seen that there is a vast difference between, say, a condition caused by the echinococcus or by the round worm, in which the effects are largely mechanical and in which little or no poison is produced by the parasite, and the disease diphtheria caused by the diphtheria bacillus, which elaborates virulent chemical poisons and causes a general *intoxication.* Some parasites also may produce a *general* infection, *e. g.* anthrax, others only a *local* infection, *e. g.* ringworm.

Parasites may therefore be divided into infective and non-infective, though there is a series of connecting links between the two, and the two groups cannot be sharply separated.[1] The *infective parasites* are: (1) Vegetable micro-organisms, bacteria chiefly, a few yeasts and some moulds; (2) many protozoa; and (3) a few metazoa, generally worms (the protozoa and metazoa are animal organisms). The *non-infective-parasites* are the animal parasites generally, particularly many worms.

The *bacteria* are minute unicellular vegetable organisms, which do not possess chlorophyl, the green colouring matter of higher plants, multiply by simple transverse division or fission (hence they are termed the *schizomycetes*), and occasionally reproducing themselves by a process known as spore-formation, in which a single small spheroidal or rounded resistant refractile body or spore is formed in the bacterial cell, which under favourable conditions will develop into the parent form. Spherical bacteria are known as *cocci*; cocci which divide irregularly, forming clusters of organisms, are *micrococci* or *staphylococci*; cocci which divide regularly and form chains are *streptococci*; if they divide into pairs or fours, as *diplococci* or *tetracocci* respectively, if in three directions in two planes of space so that cubical masses are formed, as *sarcinæ*. Straight rod-shaped bacteria are termed *bacilli*, and spiral bacteria *spirilla*; a curved rod originating by the breaking up of a spirillum is a *vibrio*, and a long, flexible spiral is a *spirochaeta*. A long filamentous form is frequently termed a *streptothrix*.[2] The bacteria are very small; a coccus is often not 1 μ in diameter,[3] a fair-sized bacillus is not more than 5–6 μ in length and 1 μ in diameter. The bacterial cells are enclosed within a membrane, which, however, does not usually consist of cellulose (as is the rule with vegetable cells), but of a modified proteid, and some are motile, moving by means of delicate protoplasmic whips or flagella.

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[1] In this section Sidney Martin's excellent classification has been largely followed, *Manual of General Pathology*, 1904, chap. iii.

[2] For further details on these and other bacteriological points consult the writer's *Manual of Bacteriology*, 2nd edition (J. & A. Churchill).

[3] μ = micron. = 0·001 mm. or $\frac{1}{25000}$ in.

The yeasts or *blastomycetes* are unicellular vegetable organisms, which are distinguished from the bacteria by the fact that they reproduce themselves by budding or *gemmation.* The cells are usually spheroidal or ovoid, occasionally elongated, have a cell membrane consisting of cellulose (which is absent from most of the bacteria), and are generally considerably larger than the bacteria, the cells measuring 10-15 μ or more in the long diameter. Under certain conditions, particularly when deprived of nutriment, many of them spore, producing three or more spores (ascospores) within the cell membrane; these are the *saccharomycetes,* or true yeasts, as distinguished from the *torulæ,* which do not spore. The blastomycetes are not of much pathological importance, but are the main agents in a number of fermentations, especially the alcoholic. Certain yeast-like forms seem to be capable of producing granulomatous neoplasms, and have been supposed to be the cause of carcinoma (see p. 67), and a variety of destructive dermatitis is caused by a yeast.

The moulds or *hyphomycetes,* a group of the true fungi, are filament-forming multicellular sporing vegetable organisms, some of which, although important as producing ringworm (*tinea*), etc., are hardly strictly infective parasites, since they are entirely local in their effects, though infectious, *i. e.* contagious. A few, however, may produce an extensive infection—*e. g. aspergillus.*

Some of the so-called streptothrix forms belong to this group.

The ringworm fungi (*Trichophyton*) are now regarded as including several species. The first variety, common in London, attacks the hair of children. The parasite forms small spores 3-4 μ in diameter and delicate mycelial threads in the hairs. It is named *Microsporon Audouini*. A second variety has large spores, is derived from man, and affects the interior of the hairs, and is known as the *Trichophyton megalosporon endothrix*, occurs later in childhood, and is not so persistent as the preceding variety. A third variety is of animal origin, the spores are large and are situated mainly on the outside of the hairs, and is hence termed the *Trichophyton megalosporon ectothrix*. It is responsible for a considerable proportion of the ringworms of the beard and nails. *Favus* and *pityriasis versicolor* are caused by somewhat similar organisms.

The bacteria, being by far the most important group of pathogenic vegetable organisms, may now be considered more in detail; but the characters exhibited by them may be applied generally, with certain exceptions, which will be mentioned, to all forms of micro-organisms, including the protozoa.

The bacteria may be artificially cultivated on a suitable nutrient soil. This for the pathogenic germs should usually contain some form of proteid, and the commercial "peptone" (really mostly albumose) is largely employed for the purpose.

A number of culture media are kept in the laboratory, the chief of which are nutrient broth,[1] nutrient agar,[2] nutrient gelatine,[3] milk, potato, peptone water (a solution of "peptone" in water), blood-serum, and solutions of various carbohydrates and alcohols in peptone water, *e.g.* glucose, lactose, cane-sugar, starch, dulcitol, mannitol, etc. The reaction of the medium is of importance, and for the pathogenic forms this is usually made slightly alkaline. Such a variety of media is not required in order to *grow* or *cultivate* the organisms; it is employed for the purpose of *differentiating species* of microbes. The organisms are so minute that they have few attributes which can be discerned microscopically, and therefore the characters of the growths on the various media, the changes produced in carbohydrates (*e. g.* acid and gas production), and pathogenic action, etc., are the main features which serve to distinguish one species from another.

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[1] Practically beef-tea with the addition of "peptone."

[2] Nutrient broth solidified into a jelly by the addition of agar, which is a substance derived from seaweed.

[3] Nutrient broth solidified with the addition of gelatin.

Most bacteria grow best at some particular or optimum temperature; for the pathogenic forms this is usually about 37° C., though most (the pneumococcus is an exception) will develop at 20° to 22° C. Growth is generally stopped if the temperature reaches 42° C. Heating for a few minutes to 60°–65° C. destroys most non-sporing forms, but spores can resist a much higher temperature (*e. g.* 80° C. for fifteen minutes), and many can be actually boiled for a short time without loss of vitality; prolonged boiling or steaming or dry heat above the boiling point sooner or later, however, destroys all forms. On this fact is based the sterilisation of instruments and dressings by heat and the disinfection of bedding and clothing of patients who have suffered from an infectious or contagious disorder. Moist heat is much more effective than dry heat, and has much greater penetrative power, and is to be preferred for sterilisation and disinfection.

Some bacteria require oxygen for their growth (aerobic forms), others will not grow if a trace of free oxygen be present (anaerobic), and others will grow either in the presence or absence of oxygen. Most pathogenic microbes are aerobic and facultative anaerobic, *i. e.* prefer oxygen, but will develop in its absence. Light, particularly sunlight, is fatal to all bacteria and their spores; it is the violet and ultra-violet rays that are the active ones. Many substances exert an inhibitory action on the growth of bacteria, and if in sufficient quantity destroy their vitality; these are the antiseptics and germicides, such as boric, salicylic, and carbolic acids, many cresols, metallic salts, particularly those of mercury, etc. All germicides in small quantity are antiseptic; but many substances, *e. g.* salt and boric acid, may be antiseptic, *i. e.* inhibit the growth of micro-organisms, without necessarily being germicidal. Moisture is also necessary for the growth of bacteria, hence desiccation prevents growth (and often destroys vitality), and is practically employed for the preservation of food-stuffs. Bacteria produce a variety of effects. Many forms will multiply only in dead organic matter and do not infect the living tissues; these are known as *saprophytes* as opposed to *parasites,* which live and grow on or in, and at the expense of, the living body. The saprophytes are of the greatest importance in Nature, since they break up dead organic matter into simpler compounds, and finally into very simple ones, water, ammonia, marsh gas, sulphuretted hydrogen, etc.; this constitutes what is known as *putrefaction,* and is usually accompanied by the evolution of foul-smelling gases containing sulphur. Many important fermentations, *e. g.* the formation of lactic and butyric acids, are also accomplished by bacteria, likewise *nitrification,* the formation of nitrates, which are essential for plant life. Substances like blood, decaying vegetable matter, and ammonia salts are valuable manures, but only through the action of bacteria, which convert them into nitrates by oxidation, and so render them available for the nutrition of plants. Pigments are also formed by many bacteria. Alkaloidal substances containing nitrogen, and other complex bodies of a toxic nature are occasionally produced by bacteria. Some of these are very poisonous and are the cause of certain forms of food-poisoning, *e. g.* by tinned foods; such are choline, neurine, mydaleine, and also tyrotoxicon (not an alkaloid, but a benzene derivative) derived from milk and cheese.

Of far more pathological importance, however, are the toxic substances elaborated by the micro-organisms; these are the essential causes of the disease symptoms. The production of the phenomena of disease by pathogenic organisms has been ascribed to (1) the using up of the oxygen which should go to the tissues; (2) the using up of the proteids of the body and of the food; (3) the effects of plugging of the vessels by the microbes; and (4) the effects of substances or "toxins," having a poisonous action, formed by the microbes. Of these, the first three are quite subsidiary, embolism and thrombosis being perhaps the most important, and it is the toxins which are the chief factors which induce the pathogenic effects. These toxins are substances of a very complex composition, probably allied to the proteids; in some instances they seem to be of the nature of enzymes or ferments, and they are direct products of the bacterial cells. With most pathogenic organisms the toxins are more or less integral parts of, and associated with, the bacterial cells, not excreted to any extent into the surrounding medium, *e. g.* typhoid and cholera; with a few the toxin is excreted, as it were, as in tetanus. Some microbes also act upon the medium, in a sense digest it, and produce poisonous albumose-like bodies.

The bacterial products are therefore classified by Sidney Martin[1] as follows:

(1) Poisons produced by the digestive or the destructive action of bacteria on proteids in the culture medium. Examples of these are the poisons of the *Bacillus anthracis* and of the pus-producing staphylococci.

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[1] *Manual of General Pathology*, p. 76.

(2) Poisons which are the result of the digestive or destructive action of bacteria on proteids but formed as an excretion (the toxin) of the bacterium. The *Bacillus diphtheriæ* is the best example of this. A similar combination of poisons is found in snake venom.

(3) Poisons which are excretions only, such as those produced by the tetanus bacillus.

(4) Poisons which are typically intra-cellular, but which may also be excretory.

The poisons produced by the typhoid bacillus, the *Bacillus coli*, the *Bacillus enteritidis* of Gaertner, and the cholera vibrio belong to this group.

The Infective Process.

With regard to the pathogenic organisms, or disease germs, Koch has laid down the following conditions, which have been termed "Koch's postulates," which must be complied with before the relation of an organism to a disease process can be said completely to be demonstrated :

(1) The organism in question must be met with in the tissues, fluids, or organs of the animal affected with, or dead from, the disease.

(2) The organism must be isolated and cultivated outside the body on suitable media for successive generations.

(3) The isolated and cultivated organism, on inoculation into a suitable animal, should reproduce the disease.

(4) In the inoculated animal the same organism must be found.

To these may be added :

(5) Chemical products with a similar physiological action should be obtainable from the artificial cultures of the micro-organism, and from the tissues of man or animals dead of the disease.

(6) A specific serum reaction, agglutinative or bacteriolytic, or both, is generally obtainable, under certain conditions, with the blood of the infected person or animal, when mixed with a culture of the specific organism producing the infection.

It is true that one or more of these conditions cannot be fulfilled in all cases, but at the same time the other conditions exist, and on general evidence the disease is classed as infective. This is the case in leprosy, for example: the *Bacillus lepræ* cannot be inoculated into animals, and it is doubtful if it can be cultivated.

The modes of infection, or entrance of the infective agent into the body, are varied. The infective agent may enter by—(1) the gastro-intestinal tract, *e. g.* typhoid, cholera, and glanders; (2) the respiratory tract, *e. g.* pneumonia and influenza, and occasionally typhoid, plague, etc.; (3) by inoculation, not necessarily only of the skin, but also of the mucous membranes —*e. g.* septic diseases generally, glanders, tetanus, etc. The extreme infectivity of some diseases—*e. g.* variola, scarlatina, influenza, etc.—may be due to the fact that infection takes place by the respiratory tract. In certain instances the infection is conveyed in some special way, *e. g.* by the mosquito in malaria and yellow fever. Nor is infection necessarily confined to one mode of entrance; in plague, for example, infection by the skin is commonest, but it is not infrequent by the respiratory, and may occur by the digestive, tract. The infecting agent may remain localised, giving rise to a *local infection,* or it may be widespread through the body, *a septicæmia*[1] or *general infection.* The absorption of chemical products from a local site of infection may produce general symptoms; this is *intoxication*, as occurs in cholera, where the microbe is limited to the bowel, in the early stage of diphtheria, where the diphtheria bacillus is present only in the membrane, and in a local abscess. Fever is usually one of the results both of intoxication and of general infection.

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[1] "Septicæmia" and "a septicæmia" mean different things. The former is applied to a general infection with the so-called septic organisms.

Infection, if recovery ensues, is generally followed by some remarkable phenomena. One of these is the production of immunity or insusceptibility to the same infecting agent. Thus, second attacks of smallpox and of scarlatina are rare; the first attack almost entirely prevents a second attack. There is great variation in this respect, however; some diseases, *e.g.* diphtheria and erysipelas, confer hardly any immunity; others, *e.g.* pneumonia and influenza, even seem to increase susceptibility; others give varying degrees of immunity. The production of immunity will be considered later.

The blood and blood-serum of an animal, or of man, which has suffered from an attack of infective disease frequently acquires the power, even when diluted, of agglutinating the infective agent. This is markedly seen in typhoid and Malta fevers; the blood-serum of the patient in a dilution of 1–20, 1–50, 1–100, or more, if added to a broth culture of the infecting microbe, the typhoid bacillus, or Malta fever coccus, causes the microbes to aggregate into large clumps and masses, agglutinates them, an effect which is not produced by the blood of an individual who has not suffered from an attack of the disease. This phenomenon forms the basis of the agglutination (or Widal) reaction, so often applied in the diagnosis of typhoid fever. The reaction of agglutination, once acquired, may persist for years—certainly three or four—and hence, in applying the test, it is necessary to exclude a previous attack. The blood of an animal injected with a few sub-lethal doses of a culture of an organism similarly acquires agglutinative properties towards the organism with which it has been injected, and this reaction (the Bordet-Durham) is made use of for the identification of bacterial species. Thus, if an organism has been isolated which is believed to be the typhoid bacillus, it may be tested with the serum of a rabbit which has been inoculated with cultures of an undoubted typhoid bacillus; if the presumptive typhoid bacillus is agglutinated thereby in high dilution, it is, in all probability, the typhoid bacillus.[1]

Another remarkable property, and one of considerable importance in immunity, conferred by the injection into an animal of complex substances, such as bacterial toxins, bacteria, blood-corpuscles, cells and cellular proteids, ferments, etc., is the development of *anti-bodies.* Thus an animal injected with sub-lethal doses of a bacterial toxin, such as diphtheria, acquires a tolerance towards the toxin, becomes immunised, and a substance is developed in the blood that antagonises the toxin which was injected; this substance is known as *antitoxin.* If bacteria be injected, the fresh blood *in vitro* has a solvent action (bacteriolysis) on the bacteria; if blood-corpuscles be injected, the blood has a solvent action (hæmolysis) on the blood-corpuscles; if cells be injected, the blood has a solvent action (cytolysis) on the cells, and so on. If ferments be injected, anti-ferments are formed and will prevent the specific action of the ferment. These phenomena may now be considered more in detail.

ANTITOXINS.—These anti-bodies produced by the inoculation of an animal with bacterial toxins or toxic proteids (*e.g.* ricin, abrin, and snake-venom) are of considerable practical importance. An animal injected with increasing amounts of the toxin acquires a high degree of immunity, and its blood-serum injected into a second animal confers on the latter a similar immunity against the toxin with which the anti-serum was prepared, but not against other toxins; the antitoxin is specific. The anti-serum formed by the injection of toxin is anti-toxic and not anti-microbic, *i.e.* does not act on the micro-organisms, is not bacteriolytic, and the diphtheria bacillus will grow and multiply in diphtheria antitoxin. Since, however, such an organism as the diphtheria or the tetanus bacillus produces its pathogenic effects mainly through the toxin which it forms, the antitoxin will counteract the effects of the *micro-organism* as well as of its toxin. The neutralisation of the micro-organism, it is true, may not be quite complete, a certain amount of local reaction or necrosis occurring. The method by which antitoxin neutralises toxin has been the subject of much discussion and research. It now seems quite to be proved that the neutralisation is a chemical one, the antitoxin combining with the toxin and rendering the latter inert, or incapable of uniting with the cells and tissues.

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[1] All these phenomena, and methods of carrying out the agglutination reaction, etc., are fully detailed in the writer's *Manual of Bacteriology,* from which the following section is largely taken.

The antidotal sera produced by the inoculation of bacterial toxins into an animal are known as antitoxins.[1]

Various theories have been advanced to account for the formation of the antidotal substances which are undoubtedly present in the therapeutic sera. Some have supposed that the toxins themselves become converted in the living body of the treated animal into the anti-bodies, but it has been proved that the quantity of anti-body formed bears no relation to the amount of toxin injected. The theory which is provisionally entertained to-day is Ehrlich's side-chain theory, which certainly explains the facts in a wonderfully simple and comprehensive manner. Ehrlich assumes that living matter, protoplasm, is composed of molecules of exceeding complexity, and bearing on them atomic groups, the "side-chains" of the organic chemist, of considerable instability, and ready to combine with other atomic groups, should these come within the sphere of action and be suited to combine with them. Such "suiting" or matching of the side-chains, such an affinity of one for the other, has been compared to the relation which exists between a lock and its proper key, or a male and a female screw. By means of these side-chains Ehrlich believes that nutrition and other chemical functions of living matter are carried out—nutrition, for example, consisting in the linking of side-chains of food-stuffs to suitable receptor side-chains of the molecules of the living matter. Similarly, he assumes that the action of a toxin, like the toxin of the diphtheria bacillus, is due to the fact that there are side-chains of the toxin molecule which are, as it were, in sympathy with, have an affinity for, side-chains of the molecules of the living cells so that the two combine. Should the living cells not possess side-chains having an affinity for the side-chains of the toxin, poisoning would not ensue—the animal would be naturally immune. The actual combination between toxin and living matter is really more complicated than this bald statement indicates, for if the action of a toxin be studied experimentally, it is found that two stages in the process of poisoning can generally be observed. For example, on injecting tetanus toxin into the blood-stream of an animal, the tetanus toxin is rapidly—in half a minute or so—taken up by the tissues of the central nervous system, and fixed there so firmly that, even if the animal be bled, the blood removed being replaced by transfusion of blood from another animal, the experimental animal still dies of tetanus. But although the tetanus toxin is thus at once fixed in the tissues, a period of many hours—it may be twenty or twenty-four—always ensues before the animal shows any signs of poisoning. This is the incubation period. Ehrlich assumes that what happens is as follows: Certain side-chains in the toxin and in the living cells have an affinity for each other, and combine; the toxin, therefore, becomes fixed to the cells. This binding of the toxin to the cells Ehrlich believes to be brought about by the combination of certain binding or "haptophore" groups of the toxin with receptor or "haptophile" groups of the cells. In order that toxic action shall ensue from such a union, a second combination between "toxophore" (*i. e.* poisoning) groups of the toxin and "toxophile" groups of the cells slowly follows, and, when complete, the symptoms of poisoning become manifest. The separate presence of these two sets of groups can be shown in various ways.

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[1] For full particulars of the preparation, mode of action, and therapeutic use of the antitoxins, etc., see the writer's *Serum Therapy* (J. & A. Churchill), price 5*s.* net; also an article by the writer in the *Pharmaceutical Journ.*, December 17th, 1904.

Production of antitoxin.—If a small amount of toxin, *i. e.* a sub-lethal dose, be injected into an animal, what happens is that the toxin unites with the living cells by combination between the binding haptophore and the receptor haptophile groups respectively of the two. Obviously, such cells as unite with the toxin are damaged, their functions must be disturbed, inasmuch as some of the atomic groups are thrown out of action, and this is manifested by some slight disturbance of the animal if the dose of toxin be small, by grave illness if it be larger, by death if it be still larger. But provided the dose of toxin be not too great, recovery ensues, rendered evident by the recovery of the animal from its indisposition; and one may legitimately assume that this recovery is attended with the reproduction by the cells involved of fresh receptor haptophile groups to take the place of those that have been put out of action, so to say, by the injection of the toxin. Supposing a second injection of toxin be given, the same process again occurs, the damage to the cells being followed by recovery, and may be repeated again and again. But it is a general physiological law (Weigert's law) that continued stimulation results in over-production—hypertrophy. This is well seen in muscles; a muscle continually called upon to perform extra work becomes enlarged—witness the massive biceps of the blacksmith; and Ehrlich believes that the same law applies to the receptor groups of the cells. As a consequence of the continued stimulation of repeated injections of toxin, the cells begin to reproduce haptophile or receptor groups in excess, more than are sufficient to replace those that have combined with the haptophore groups of the toxin, and ultimately this goes on to such an extent that these receptor groups can no longer all remain attached to the cells; they are cast off, excreted, as it were, and float free in the blood. These free receptor groups, Ehrlich conceives, constitute the specific anti-bodies, the antitoxic substances. From this theory of the genesis of antitoxin, its mode of action in neutralising and rendering inert toxin, and in the treatment of disease, becomes clear. Normally, for a toxin to produce its poisonous effect it is necessary for it first to become linked to the cells by the union of *its* haptophore groups with *their* receptor groups. But if a toxin come in contact with its homologous anti-body or antitoxin in the blood, its haptophore groups unite with the receptor groups of the anti-body, and the toxophore or poisoning groups of the toxin, though still present, can no longer exert their toxic action, because the first essential necessary—the fixation of the toxin to the cells by the combination of the haptophore and receptor groups—is no longer possible, the haptophore groups of the toxin already being saturated by the specific anti-body in the blood. In disease, therefore, by injecting antitoxin, the anti-bodies unite with the toxin, prevent the latter from uniting with the cells, and so render the toxin inert.

ANTI-MICROBIC SERA.—If an animal be injected with increasing doses of bacteria, care being taken to keep below a lethal dose, the animal becomes gradually accustomed to the microbe and ultimately acquires a high degree of immunity, so that it is unaffected by amounts which would infallibly kill an untreated animal. Moreover, the blood-serum of such a treated animal if injected into a second animal will protect the latter against a few lethal doses of the microbe, but not against a large amount. Nor is the protection afforded proportional to the amount of serum injected; for example, if 0·02 c.c. of anti-cholera serum will protect against 1 mgrm. of living cholera culture, three times as much, or 0·06 c.c. of the serum, will not protect against 6 mgrm. of cholera culture, and when a certain dose of the culture is reached, no amount of serum will save the animal. The mode in which the serum acts may be studied microscopically. If cholera anti-serum and cholera culture are injected into the peritoneal cavity of a guinea-pig, and if the peritoneal contents be examined at short intervals afterwards, it will be found that the vibrios first lose their motility, then become distorted in shape, undergo solution, and finally disappear. The protection afforded by the anti-serum is therefore due to the destruction of the microbes by solution, the process being known as "bacteriolysis," and the bodies which bring it about being termed "lysins." The reaction is known as "Pfeiffer's phenomenon" or reaction, from its discoverer. If the serum and the microbes be mixed *in vitro*, the latter are unaffected; apparently, therefore, some constituents of the living body in addition to the anti-serum are necessary for the solution of the microbes. But in 1895 Metchnikoff showed that the reaction would take place *in vitro* provided that some of the fresh peritoneal exudate of a normal guinea-pig were added to the mixture of anti-serum and microbes. The same year Bordet found that the addition of the peritoneal exudate was unnecessary provided the anti-serum were perfectly fresh. These experiments prove that the solution of the microbes is brought about by the interaction of at least two substances, one of which is present in the fresh serum and in the living body, but is unstable and rapidly disappears from the serum, the other is a relatively stable body produced during the process of inoculation. The former, the unstable body present in the normal animal, is usually termed the "complement," while the stable constituent is known as the "immune body." These considerations suggest an explanation of why it is that the anti-microbic serum will only neutralise a certain amount of living culture—viz. that only a limited amount of complement is present in the body, and when this has been used up no further bacteriolysis can occur. Attempts to employ anti-sera for the treatment of cholera, typhoid, plague, etc., have been relatively unsuccessful, probably on this account. These sera are anti-microbic, and fail to act owing to insufficiency of the complement. Wassermann has attempted to supply this deficiency by injecting *fresh* ox serum together with the immune anti-serum.

HÆMOLYSIS.—Some blood-sera possess marked powers of dissolving the red blood-corpuscles of another species, and of setting free their contained hæmoglobin (*e.g.* goat serum dissolves rabbits' and guinea-pigs' corpuscles); and if an animal be injected with the blood-corpuscles of another species, its blood-serum generally acquires the property of dissolving the blood-corpuscles with which it has been injected. For example, the serum of a normal guinea-pig has no hæmolytic action upon the red corpuscles of the rabbit; but if a guinea-pig receive a few injections of defibrinated rabbit's blood, its blood-serum acquires hæmolytic properties and dissolves the red corpuscles of the rabbit. This solution of the blood-corpuscles is termed "hæmolysis," and the substances which produce hæmolysis are "hæmolysins." If the active serum be heated to 56° C., it loses its hæmolysing power, but can again be rendered hæmolytic, be "activated," by the addition of *fresh* normal serum, normal serum, however, rapidly losing its activating properties on keeping. It will thus be seen that there is an almost complete analogy between bacteriolysis and hæmolysis, the latter being brought about by the interaction of two substances, one specific and stable, produced by the injections, the "immune body," and the other an unstable body present in fresh normal serum, the "addiment" or "complement."

Hæmolysis plays a considerable part in many infective diseases, *e.g.* septicæmia, pyæmia, malaria, etc., and in pernicious anæmia, and hæmolysins can be detected in many bacterial cultures.

Cytotoxins.—Analogous to the hæmolysins or hæmotoxins, anti-sera may be prepared which have a destructive action upon cellular elements; these are termed "cytotoxins." The formation and mode of action of these cytotoxins resemble those of the hæmolysins, and their study and preparation open up possibilities in the way of treating such diseases as carcinoma and sarcoma.

ANTI-FERMENTS.—By the injection of rennin or other enzyme the blood-serum of the treated animal acquires the property of neutralising the action of the enzyme with which the animal has been inoculated. Thus, if rennin and anti-rennin (the serum of an animal injected with rennin) be mixed with milk, no curdling takes place.

IMMUNITY.

No fact in biology is more striking than the differences in susceptibility to disease conditions exhibited by different races and different animals. For example, the native races in many parts of the world are comparatively insusceptible to yellow and enteric fevers and malaria, the dog and goat are rarely affected with tuberculosis, and tetanus is never met with in the fowl; and, to come nearer home, while some individuals are lucky enough to escape most of the commoner infectious fevers, others seem to contract them on every possible occasion, and to suffer from all the ills that flesh is heir to. These instances show that there is often a natural insusceptibility to infective disease, or a natural immunity, as it is termed, either complete, or partial and appertaining to the race—"racial immunity," or varying in different individuals and at different ages, "individual immunity," as in the case of diphtheria and scarlatina, which become more and more rare as age advances.

Still more striking, perhaps, is the fact that an insusceptibility may be acquired either after an attack of infective disease or, in certain instances, by inoculation. Thus second attacks of smallpox and scarlatina are rare, while inoculated smallpox and vaccinia protect against variola. These are examples of an acquired insusceptibility or acquired immunity.

With regard to the immunity of native races to certain diseases, this is probably due to natural selection and heredity. During long periods of time, the individuals being all exposed to the same risks, the susceptible ones are weeded out, while the survivors transmit their insusceptibility to their descendants; but this, of course, does not explain the reason for the relatively greater immunity of the insusceptible individuals. Various factors doubtless conduce to natural immunity. Frogs, fish, and chicken are naturally immune to anthrax. In the one case the body temperature is low, 18° C. or thereabouts; in the other it is high, 40° to 41° C., and this may influence the growth of the anthrax bacillus, preventing the full and rapid development which may be necessary for the production of the disease. That such is the case would seem to be shown by experiments in which if the temperature of the medium is raised or lowered, infection takes place; frogs and fish kept in water raised to a temperature of 35° C., and chicken refrigerated so as to reduce their temperature, all perish from anthrax after inoculation. That this, however, is not necessarily the only factor is certain; for sparrows, which have a temperature as high as that of chicken, can be infected with anthrax without refrigerating. Immunity is probably never absolute—that is, infection can usually be induced under certain conditions. Thus fowls, which are highly refractory to tetanus and tolerate considerable doses of tetanus toxin with impunity, can be tetanised with large doses of an active toxin; white rats, which are insusceptible to anthrax, become susceptible after fatigue, or when fed exclusively on a vegetable diet.

Behring would ascribe the immunity of white rats to anthrax to the high alkalinity of their blood, and claims to have shown experimentally that a vegetable diet reduces this, and fatigue is said to act similarly.

Ehrlich's side-chain theory suggests a simple explanation of natural immunity. In order that a bacterial toxin may produce intoxication it must become anchored to the cells by its haptophore group, and that this may occur the cells must possess atomic groups or side-chains ("receptor groups") which have a special affinity for the haptophore groups of the toxin. Should these be wanting, the toxin cannot become anchored to the cells, its toxophore groups cannot exert their influence, and natural immunity is the result.

The blood, lymph, and other fluids and tissue juices undoubtedly exert more or less germicidal action on bacteria experimentally *in vitro* and probably also in the body. But in this respect there is often a marked difference between the circulating blood and the blood *in vitro*, and it is doubtful if this factor is of great importance in the production of natural immunity.

An important theory of immunity is the doctrine of phagocytosis, so ably supported by Metchnikoff. This is the "cellular theory of immunity." It has as its basis the following fundamental facts: Firstly, the leucocytes in the circulating blood ingest and destroy any foreign particles injected; secondly, any injury to the tissues is immediately followed by an inflammatory reaction, in which the leucocytes emigrate from the vessels and congregate at the injured spot. Similarly, in many instances the leucocytes rapidly congregate at the seat of a bacterial infection, and approach and engulf the bacteria in the same manner as they do other foreign particles, and so rid the body of the intruders.

The migration of the leucocytes towards the scene of action is explained by Metchnikoff on the hypothesis that the chemical substances elaborated by the bacteria attract the latter and exert what he termed "positive chemotaxis." In this case the bacteria are removed by the leucocytes, and general infection and death do not occur. Unfortunately in other cases the bacterial products repel, or at least do not attract, the leucocytes and "negative chemotaxis" occurs, so that the bacteria are free to grow and multiply, and general infection ensues. Positive and negative chemotaxis can be shown to occur by a simple experiment. If a fine capillary tube containing some peptone solution be introduced into an emulsion of bacilli, *e. g. B. fluorescens liquefaciens*, under a cover-glass, and watched microscopically, the bacilli will be attracted to the tube and soon invade its lumen. If, however, a weak acid be substituted for the peptone water, the bacilli will be repelled. The process by which the bacteria are engulfed by the leucocytes can be similarly watched. The leucocytes which act in this manner are termed "phagocytes," and they are of two classes—the macrophages, the large mononuclear leucocytes, and the smaller microphages, or polymorphonuclear leucocytes. Certain of the tissue-cells and endothelial cells also possess phagocytic properties. That an acquired immunity may be due to the education of the leucocytes seems to be shown by the fact that, while in ordinary susceptible rabbits infection with anthrax is followed by a feeble phagocytosis and the animals succumb, in vaccinated rabbits phagocytosis is very active. Moreover, in an animal refractory to anthrax, such as the frog, if the bacilli be enclosed in minute bags of paper or membrane, so as to prevent the access of the phagocytes, the bacilli grow and multiply. An immense amount of experimental proof has been obtained by Metchnikoff and his pupils of the truth of the doctrine of phagocytosis, but in spite of their ingenuity the theory has not a universal application, and phagocytosis *alone* will not explain many cases of immunity. However, as Metchnikoff observes, under natural conditions it is against the penetration of the *micro-organisms* that the animal must be protected.

Many cellular proteids and nucleins are germicidal, and to these germicidal constituents Hankin gave the name "alexins," and the suggestion has been made that in phagocytosis, the amœboid cells having been attracted to the point of attack, the invading bacteria are destroyed by nucleins (or their precursors) either secreted by, or formed by the disintegration of, the amœboid cells. Observations of Kanthack and Hardy support this view. They found that the coarsely granular oxyphile leucocytes (which are not markedly phagocytic) are attracted to the site of a bacterial invasion and there discharge their oxyphile granules, and the bacteria then begin to show signs of degeneration. The phagocytes proper, which up to now have remained quiescent, then approach and engulf the bacteria. By these observations the cellular and humoral conceptions of immunity may be combined, and we arrive at a "cellulo-humoral" or "alexocyte" theory of immunity. The alexins, whatever their nature, it can hardly be doubted are products of the leucocytes; the leucocytes are attracted to the seat of attack, and there, by secretion or disintegration, set free the active alexins, which are powerfully bactericidal and cause the dissolution of the bacteria.[1] Metchnikoff has so far modified his theory as to admit that destruction of bacteria in phagocytosis is brought about by chemical bacteriolytic substances, which he terms "cytases," and which he regards as being derived from the leucocytes, and to be identical with the alexins.

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[1] See Bulloch, *Brit. Med. Journ.*, 1904, vol. ii, p. 560.

A quantitative method for estimating phagocytic power has been devised by Leishman. A thin emulsion of some micro-organism, *e.g. S. pyogenes aureus*, is mixed with an equal volume of blood from the finger, a droplet of this mixture is placed on a clean slide, and covered with a cover-glass, and the preparation is at once placed in a moist chamber in the incubator at 37° C. for half an hour. At the end of this time it is taken out, the cover-glass slipped off, and the films on slide and cover-glass are dried, fixed, stained, and examined microscopically, and the number of microbes ingested by the polymorphonuclear leucocytes counted.[1]

Recently Wright and Douglas[2] have found that the washed leucocytes without serum are non-phagocytic, but become so on the addition of normal serum. If, however, the serum be first heated to 60–65° C. before being added to the mixture of leucocytes and microbes, phagocytosis does not take place, but if the unheated serum is mixed with the bacteria kept at 37° C. for fifteen minutes and the mixture is then heated to 60° C. for fifteen minutes, phagocytosis can still take place, thus demonstrating that the serum acts in some way on the bacteria, rendering them suitable prey for the phagocytes. This thermolabile serum feast preparer is called by Wright and Douglas "opsonin" (from a word meaning to cater for).

They have also shown that during the process of active immunisation the opsonic value of the serum is increased, and they have succeeded in demonstrating this opsonic immunity for a number of infections, such as the staphylococcus, Malta fever, pneumococcus, and tubercle. Bulloch and Atkin have been able to confirm the work of Wright and Douglas, and have studied in other directions the mode of formation and action of opsonic sera.

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[1] *Brit. Med. Journ.*, 1902, vol. i, p. 73.

[2] *Proc. Roy. Soc. Lond.*, vol. lxxii, 1903, p. 357; and *ibid.*, vol. lxxiii, 1904, p. 128.

Acquired immunity may be induced in many ways:

(1) By an attack of the disease ending in recovery.

(2) By vaccinating with a modified and less virulent form of the living infective agent (Pasteur's method).

(3) By one or more treatments with sterilised cultures, or bacteria-free toxins.

(4) By injection of the blood-serum from an animal treated or immunised by method 3.

(5) Occasionally by treatment with sterilised cultures or toxins of a different species (*e.g. B. pyocyaneus* protects from anthrax).

Various explanations have been given of the production of acquired immunity. Pasteur suggested that an organism, by its growth in the body, exhausted some specific pabulum necessary for its development, so that the same organism could not again grow in the animal which had been attacked. This hypothesis, therefore, presupposes that in the body there is some nutrient material necessary for the growth of every species, which is difficult to believe, and is negatived by the fact that an organism will grow in the blood and tissues removed from an animal vaccinated against, and insusceptible to, the disease produced by it. Chauveau in his retention theory suggested that the bacteria during their growth in the tissues formed substances which ultimately inhibited their growth, and, if the animal recovered, prevented a subsequent development of the organism.

The "education" of the leucocytes whereby they are attracted, instead of being repelled, by a bacteria invasion, may be the result of an attack of infective disease ending in recovery, and so "acquired immunity" from the particular infection be brought about.

Ehrlich by his classical experiments with abrin and ricin, two toxic proteids obtained from the jequirity and castor oil beans respectively, showed that acquired immunity is of two kinds, one "active," as he termed it, of long duration, and resulting from an attack of the disease, or vaccination with a modified virus and not transmissible to the fetus; the other "passive," resulting from the inoculation of an animal with the blood-serum (antitoxin or anti-microbic serum) derived from another animal immunised by the injection of bacterial toxins. "Passive immunity" is soon lost, but while present is transmitted to the fetus.

Acquired immunity may be induced by inoculation with increasing quantities of bacterial toxins, as in the treatment of an animal for the production of antitoxin. The animal finally acquires a high degree of immunity, which is transmitted to the fetus through the blood of the placental circulation and to the nursling through the milk.

Natural immunity in most cases is certainly not due to the presence of antitoxins; for example, the blood of the fowl, a bird which is highly insusceptible to tetanus, has not the slightest antitoxic power towards a tetanus toxin. Moreover, in the preparation of an antitoxin by injecting an animal with toxins, the immunity towards the toxins gradually increases, and *pari passu* the antitoxic power of the serum increases up to a certain point, but then slowly and steadily falls, until it is almost lost, yet the animal remains as highly immune as ever.

To sum up, natural immunity is probably due to a number of factors, some or all of which may be operative in particular instances, and it is impossible to state with certainty any general law. In general, phagocytosis is the most powerful means of defence; in others the fluids of the body may exert a germicidal or inhibitory influence upon the bacteria, the germicidal constituents in all probability being derived from leucocytes or other cells; in others, again, the cells and tissues for some reason are unaffected by the bacterial toxins, perhaps because the cells are lacking in the particular side-chains or receptors, which have a special affinity for the toxins.

As regards the immunity acquired after an attack of disease, this may be due to the "education" of the leucocytes, whereby they are attracted, whereas formerly repelled, by the products of bacterial development. The germicidal and inhibitory actions of the body fluids may also be enhanced. There is also a possibility that the side-chains or receptors having an affinity for the toxin become in some way destroyed or used up, so that no further fixation of the particular toxin can take place. "Thousands of facts point to the conclusion that our leucocytic-forming tissues are our great defensive organs against parasitic invasions. The mystery is how the microbes are destroyed, and in this connection we seem pretty much in the same state as John Hunter, over a century ago, when he wrote of pus: 'The final intention of this secretion of matter is, I believe, not yet understood, although almost every one thinks himself able to assign one, and various are the uses attributed to it.' "[1]

THE PRINCIPAL INFECTIVE DISEASES, AND THE MICRO-ORGANISMS WHICH PRODUCE THEM.

The infective diseases are described as acute or chronic, according to the duration; but one merges into the other, and a disease is sometimes acute and sometimes chronic, *e. g.* tuberculosis, or may have acute exacerbations.

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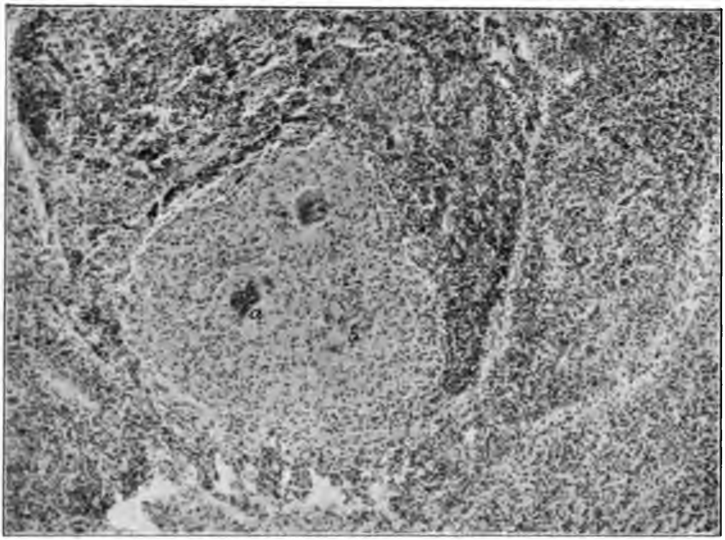
[1] Bulloch, *loc. cit.*

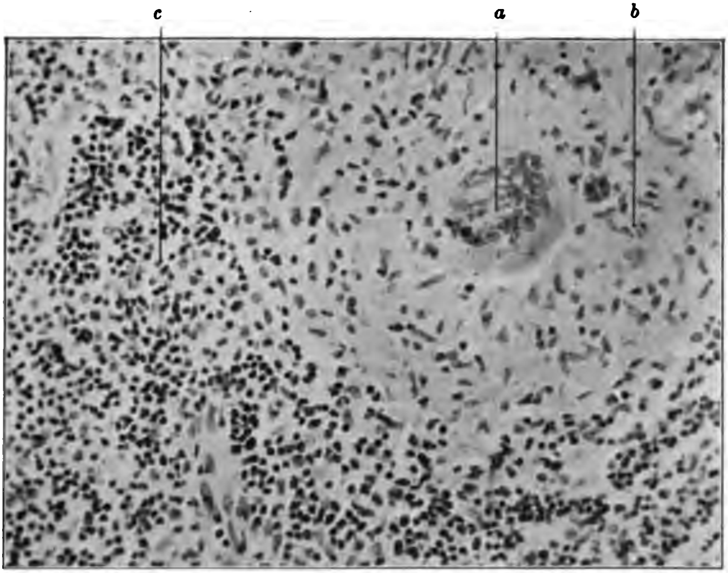
Some of the infective diseases are characterised by the local proliferation of cells with the formation of cellular nodules, which, from their resemblance to granulation tissue, have been termed *granulomata,* and the diseases in which they occur, the *infective granulomata.* Such are tuberculosis, syphilis, leprosy, glanders, and actinomycosis, which may first be considered.

TUBERCULOSIS.—Histologically, tuberculosis is characterised by the formation of cellular nodules—the "tubercles," which, when fully formed, are about the size of a small pin's head and translucent and greyish in appearance. Microscopically, one or more giant cells are usually present near the centre (Plate VIII., A. and B., *a*). These are irregular cells of very large size, with ten to twenty nuclei disposed round the periphery. Their origin is uncertain, but they are generally regarded as being produced by fusion of smaller cells, and to be defensive and phagocytic in nature, since tubercle bacilli occur within them. Though very characteristic of tuberculosis, they are by no means peculiar to this disease, being met with in other granulomata, in tumours, and occasionally in inflammation. Around the giant cells a zone of well-marked cells with large and distinct nuclei is present; these are the epithelioid cells, so called from their resemblance to epithelium, or, as they are now termed, the endothelioid cells (Plate VIII., A. and B., *b*), and are probably derived from endothelial and connective-tissue cells. They are surrounded by a zone of smaller cells with less distinct nuclei—the lymphoid cells (Plate VIII., B., *c*), which are probably derived from the blood and lymph tissue. In chronic

PLATE VIII.



A. A young tubercle. *a.* A giant cell. *b.* Zone of endothelioid cells. (Hæmatoxylin and orange rubin, × 40.)



B. A young tubercle, the same as A more highly magnified. *a.* A giant cell. *b.* The zone of endothelioid cells. *c.* The zone of lymphoid cells. (× 100.)

tuberculosis plasma-cells are also present. In the young tubercle blood-vascular channels are present, but these soon become occluded by endothelial proliferation and thrombosis, and the central portion of the tubercle undergoes necrosis and caseation. Around the tubercle, particularly if chronic, a layer, more or less complete, of fibrous tissue often forms, and is an important factor in the healing of the tubercle. More or less tissue reaction, seen as hyperæmia and round-celled infiltration, surrounds the tubercle.

Tuberculosis frequently attacks the lungs (phthisis), the glands, particularly of the neck (scrofula), and the intestine; it also occurs in other parts. Infection in phthisis probably takes place by the respiratory tract, in the cervical glands by way of the tonsils, and in the intestine by material swallowed, *e. g.* tuberculous sputum or milk. A general infection is not uncommon, especially in children—*acute miliary tuberculosis.* Once infection has occurred, it spreads locally by contiguity, and to distant parts chiefly by the lymphatics, sometimes by the blood-stream.

The specific organism, the tubercle bacillus (*B. tuberculosis*), which is present in varying numbers in the tuberculous lesions, is a minute slender bacillus 3–5 μ in length, often presenting a beaded or segmented appearance, "acid-fast," *i.e.* when stained with fuchsin retains its colour after treatment with 25 per cent. sulphuric acid, a procedure which removes the colour from most organisms. It is difficult to cultivate and grows slowly, forming on glycerine agar a dryish, crinkled, skin-like growth. From broth cultures tuberculin is prepared by extraction and concentration. The bacillus is readily inoculable in a number of animals, producing typical tuberculosis. There seem to be varieties of the organism, *e. g.* the mammalian and avian, but there is no essential difference between the human and bovine bacilli, though Koch stated the contrary.

Lupus is a superficial eroding, chronic tuberculosis of the skin and mucous membranes, as is proved by inoculation experiments, but bacilli are very difficult to find in the typical tubercles which are present.

LEPROSY is also distinguished by the formation of nodules in the tissues. These are commonly situated in the skin, subcutaneous tissue, and mucous membranes, particularly of the nose, giving rise to the nodular (tubercular) variety of the disease. They also develop in the peripheral nerves, causing anæsthesia (the anæsthetic variety), and in the internal organs.

The leprous nodule is a granuloma made up for the most part of endothelioid cells, with occasional giant cells. Necrosis occurs, and ulcers form, but caseation does not take place.

The specific organism, the leprosy bacillus (*B. lepræ*), is very like the tubercle bacillus in morphology and staining reaction, but is non-inoculable on animals, and is non-cultivable (with doubtful exceptions). It is present in extraordinary numbers in the tissues, particularly in the skin, the disease differing in this respect markedly from tuberculosis. The bacilli are aggregated in large rounded clusters, or groups, within the so-called leprous cells, which are probably in reality the lumen of lymphatic vessels in cross-section, crowded with bacilli.

SYPHILIS.—The primary lesion appears at the site of inoculation in the form of the Hunterian chancre or hard sore. This commences first as a papule or excoriation, but by cell-proliferation a nodule is formed consisting of lymphoid and endothelioid cells, with larger, and not infrequently with giant, cells, which soon undergo necrosis with ulceration, or the ulceration may be present from the first and the base of the ulcer become infiltrated. By ulceration the greater part of the granuloma is ultimately removed, but some cicatrisation remains. In the later stages plasma cells and fibroblasts become numerous. A certain time after the primary sore secondary symptoms and lesions ensue, viz. fever, rashes, and inflammation of lymph-glands, skin, and mucous membranes. The syphilitic *condyloma* is a raised patch of skin or mucous membrane, produced by infiltration of the papillæ with round cells and liquid exudation, causing swelling and prominence of the epithelium and corium over them, the cutis becoming sodden and gelatinous.

Later still tertiary phenomena appear in the form of inflammations of the viscera and bones, and particularly the development of granulomata known as *gummata*, which occur principally in the viscera, the brain and its membranes, and periosteum. The gumma consists of a mass of cells, very like those of the condyloma, and of newly-formed vessels. The latter soon undergo obliteration from a syphilitic endarteritis, and necrosis of the mass and fatty degeneration and caseation ensue, and may result in ulceration or suppuration. More or less absorption may occur with the development of fibrous tissue and the ultimate formation of a puckered stellate cicatrix; this is frequently met with in the liver.

Sometimes the syphilitic inflammation causes a generalised round-celled infiltration, with the subsequent development of fibrous tissue with which the organ becomes permeated, as in the lung and liver.

The micro-organism of syphilis is unknown. Recently long spiral organisms (*Spirochaeta pallida* of Schaudinn) have been detected in the lesions. The disease is inoculable only on man and apes.

Glanders is a disease primarily of equines, but communicable to man. In the horse the lesions are always present in the lungs, and frequently in the nasal mucous membrane. When, in the horse, the lymphatic glands and vessels are affected, the disease is known as farcy.

The lesions in the lungs of the horse consist of hard shotty nodules, in the early stages consisting of endothelioid-like cells, which in reality, however, are almost entirely polymorphonuclear leucocytes.[1] These soon undergo the form of degeneration and necrosis known as chromatotexis (Unna), which consists in a disorganisation of the nuclei, the cell-body remaining intact, and the fragments of chromatin, resulting from the nuclear disintegration, retain for a considerable period their affinity for nuclear stains. In consequence, the centre of the glanders nodule becomes darkly stained even when necrosis is complete and all structural detail obliterated.

In chromatotexis the chromatin fragments are at first for the most part spherical, but later, when necrosis is complete, and the cell-bodies are indistinct, many of them become elongated and swollen at the ends. Unna states[2] that there is no leucocytic infiltration around the glanders nodule in the human subject, and that the bacilli appear to be chemotactically indifferent to wandering cells, but according to McFadyean the very reverse of this is the case in the horse. In this animal, the young nodule has a peripheral zone marked by the effusion of a fibrinous exudate or of actual blood; in the older nodules there is a thin peripheral capsule of young fibrous tissue, between which and the central leucocytic area is a zone of endothelioid cells, in which giant cells may be seen. Unlike a tubercle, giant cells are never present in the centre of the nodule.

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[1] See McFadyean, "Harben Lectures," *Journ. State Med.*, 1905, January, February, and March.

[2] *Histo-Pathology of the Diseases of the Skin*, Eng. ed., p. 462.

The specific organism, the glanders bacillus (*B. mallei*), is a small bacillus 2–5 μ in length, and a little thicker than the tubercle bacillus, not acid-fast and non-Gram-staining. On potato it forms raised shining drops at first like honey, subsequently becoming chocolate-brown. Inoculated into a male guinea-pig, it produces characteristic enlargement of the testes (Straus's test). The bacillus is difficult to demonstrate by staining methods in the tissues. Mallein is a fluid obtained by boiling, concentrating, and filtering broth cultures, and is used for the diagnosis of the disease in animals. In a glandered horse the injection of mallein is followed by a swelling at the seat of inoculation and rise of temperature.

Glanders is transmissible by ingestion and by inoculation; natural infection in the horse is probably usually by ingestion. In man also infection may probably occur in both ways; the disease is often characterised by intra-muscular abscesses.

ACTINOMYCOSIS.—This is a disease both of animals (oxen) and of man, characterised by the formation of granulomata, which soon break down with suppuration and abscess formation. The granuloma is composed of a round-celled infiltration at first principally of lymphocytes, subsequently of polymorphonuclear leucocytes as well; scattered through the central portion of the granuloma are masses of the organism, the ray fungus. Giant cells may be present and contain the organism. Around the granuloma an inflammatory zone of round and plasma cells develops, and the mass may become encapsuled in fibrous tissue and the central portions become calcified. The lesions are met with in the tongue and jaw, in the digestive tract, in the lungs and pleura, and occasionally in the skin.

The actinomyces or ray fungus is a streptothrix form, or perhaps a true fungus. The organism occurs in the tissues of the ox as an irregular or reniform mass of radially disposed club-shaped structures (hence the name ray fungus), which stain well by Gram, the central portion not staining, but in man usually as a little mass of tangled filaments, staining by Gram. The clubs, however, are present as in the bovine variety, but are stunted and inconspicuous, and do not take the Gram stain, though easily seen in fresh preparations.

The organism (*actinomyces*) forms in cultures masses of filaments staining by Gram, and producing dense, tough, brownish, raised growths, which when old become yellowish, as though powdered with flowers of sulphur.

The condition (*actinomycosis*) clinically resembles tuberculosis closely, but in the pus sulphur-yellow grains occur, the size of a small pin's head, which are the masses of the organism. There are probably several species of *actinomyces*, and actinomycosis, therefore, is a clinical group of diseases closely resembling one another. Another condition met with in India, Madura foot, is due to a somewhat similar organism.

Septic Diseases and Suppuration.

Under the terms "septic diseases" and "suppuration" are included abscesses, boils and carbuncles, cellulitis, osteomyelitis, erysipelas, gonorrhœa, infective endocarditis, pyæmia, septicæmia, and sapræmia, puerperal fever, and hospital gangrene.

By "sapræmia" is meant the constitutional condition arising from the absorption of the toxic products elaborated by the micro-organisms of sepsis, the latter being localised and absent from the general circulation. In the acute form it is not a common condition, the best example being that which occurs after parturition; by simply clearing and washing out the uterus the symptoms rapidly abate. In septicæmia not only is there usually a local site of infection, but in addition micro-organisms are present in the general circulation. It is true they are not abundant in the latter situation, and Cheyne[1] believes that they are to a large extent arrested in the capillaries; staphylococci and streptococci are the commonest forms. Pyæmia is characterised by the presence of micro-organisms, most frequently streptococci, in the general circulation, and in addition by the formation of abscesses in various situations. These arise usually from suppurative phlebitis with the formation of septic emboli and thrombi. The sequence of events, according to Cheyne (*loc. cit.*, p. 603), is (*a*) phlebitis in direct connexion with the wound, (*b*) a thrombus impregnated with micro-organisms is formed in the vein, (*c*) this softens and disintegrates, and particles or emboli are carried to distant parts, (*d*) these lodge in the capillaries, with the formation of infarctions and abscesses. Suppurative pylephlebitis is a pyæmia affecting the portal system of vessels. As regards the so-called chronic pyæmia or multiple abscesses, Cheyne considers that it differs from true pyæmia in that embolism plays no part. Organisms gain access to the blood-stream, settle in any spot where the vitality of the tissues is depressed, grow and multiply, and there produce an abscess.

The mere presence of organisms is not everything; injury, thrombosis and embolism, and lowered vitality are all important contributing factors. It can hardly be doubted that micro-organisms are continually passing into the blood and organs, where they are, fortunately, as a rule disposed of. But if, for example, the endocardium has been damaged by the rheumatic inflammation, should the *M. pyogenes aureus* or the streptococcus happen to come into contact with the damaged surface, it may obtain a foothold and convert the simple inflammation into an infective one, and infective or ulcerative endocarditis is the result.

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[1] Clifford Allbutt's *System of Medicine*, vol. i, p. 597.

The micro-organisms associated with these conditions are very varied. The principal are the group of staphylococci, the streptococcus, the *Diplococcus pneumoniæ, B. coli, B. pyocyaneus,* the gonococcus, and the typhoid bacillus, and several other species are of occasional occurrence.

Of the staphylococcus group, the *M. pyogenes aureus* is the most important. This is a micrococcus 0·5–1 μ in diameter, growing freely and rapidly, producing on agar and potato orange-coloured growths much like a streak of oil-paint, and rapidly liquefying gelatin. It is met with on the skin, in boils and carbuncles, in localised abscesses and superficial ulcers, and frequently in septicæmia, pyæmia, osteo-myelitis and infective endocarditis. The *M. pyogenes albus* and *citreus* are of occasional occurrence in abscesses, etc., but are usually less virulent than the *aureus,* from which they are distinguished by the colour of their growths, white in the one case and lemon-yellow in the other. A variety of the first named, the *M. epidermidis albus* of Welch, is common on the skin, and is a frequent source of stitch abscess. Two or more of these species may be associated. Another group of staphylococci also occurs, the *M. cereus albus,* etc., the members of which do not liquefy gelatin, and are not of much practical importance.

The *Streptococcus pyogenes* vel *erysipelatis* is an important organism. It is a chain-forming coccus, 1 μ in diameter, forming a delicate punctate growth on agar and on gelatin without liquefaction of the latter. There are several varieties, if not species, of this organism, characterised by minute differences in cultural characters and by the length of the chains.

It occurs in acute abscesses, in erysipelas, in spreading or phlegmonous inflammations, such as cellulitis, and in septicæmia, pyæmia, infective endocarditis, etc.

The *Diplococcus pneumoniæ,* Fraenkel's pneumococcus, is a small, somewhat elongated or lance-shaped coccus occurring in pairs, occasionally in short chains of four. It is the cause of acute croupous pneumonia, and is found in great abundance in the diseased lung and in the expectoration, in both of which it is surrounded by a capsule. It grows on agar and on serum at blood heat, forming an extremely delicate greyish film, but does not grow on gelatin at room temperature. On cultivation it loses its capsule and forms short chains, so that it is in reality a short streptococcus (*S. brevis* variety). It can produce suppuration, *e. g.* empyema, and occurs in some cases of meningitis, arthritis, and peritonitis. All the above-named forms stain by Gram.

The *Bacillus pneumoniæ* of Friedländer is quite a different organism. It is in its cultural characters allied to the *B. coli,* and is occasionally met with in bronchitis, angina, etc.

The *M. gonorrhœæ,* the specific organism of gonorrhœa, an infective inflammation of the urethra and other mucous membranes, is a minute coccus, in shape like a coffee-bean, and occurs in pairs, occasionally in tetrads, in groups of several within the pus-cells. It does not stain by Gram, and grows only on serum or on blood-agar. It is also met with in oöphoritis, salpingitis, gonorrhœal arthritis, and a few cases of infective endocarditis and of general infection have been described.

EPIDEMIC CEREBRO-SPINAL MENINGITIS, spotted fever, is caused by the *Micrococcus intra-cellularis* of Weichselbaum. It is a small coccus, occurring in pairs or tetrads within the pus-cells of the exudation. It does not stain by Gram, and grows freely on agar at blood heat, a feature distinctive from the gonococcus.

The bacillus of malignant œdema is a long or thread-forming, sporing, anaerobic, non-Gram-staining bacillus, associated with an intense necrotic inflammation and emphysematous gangrene, such as attack contused or lacerated, dirty wounds.

The *B. aerogenes capsulatus* is a large Gram-staining anthrax-like bacillus, also producing emphysematous gangrene and gas-production in the blood and internal organs, *e. g.* "foaming liver."

The *B. pyocyaneus* is a small motile non-Gram-staining bacillus, the cause of "blue-pus." It produces a fluorescent bluish-green colour in agar and in gelatin; the latter it rapidly liquefies. General infection occasionally occurs (*maladie pyocyanique* of the French), and it is met with in marasmus and in certain cases of dysentery.

DIPHTHERIA.—Diphtheria is caused by the *B. diphtheriæ* of Klebs and Löffler, frequently therefore termed the Klebs-Löffler bacillus. It is a delicate rod 3–5 μ in length, and presenting considerable irregularity in form, *e. g.* segmentation of its protoplasm and club- and spindle-shaped involution forms. It is non-motile, non-sporing, stains well with methylene blue and by Gram, and grows best on serum. In cultivation (also in the membrane) there is a marked tendency to a parallel grouping. In the diagnosis of diphtheria a piece of the membrane or a swabbing from the throat is rubbed over the surface of a serum tube, which is then incubated at blood heat for sixteen to twenty hours or thereabouts and the growth examined microscopically.

Diphtheria is primarily a local disease of the mucous membrane of the pharynx, larynx, and nose, from whence it may spread to neighbouring parts. It also attacks wounds, the conjunctiva, vulva, etc. Infection is followed by inflammation and fibrinous exudation, the latter, with coagulative necrosis of the underlying mucous membrane, forms the tough wash-leather-like diphtheritic membrane (Fig. 8), and on separation leaves a bleeding patch. In cases which are at all severe and have lasted more than a day or two, more or less general infection ensues, and the bacillus can be isolated from the lungs, kidneys, etc., and visceral lesions are common, necrotic foci in the liver, catarrhal nephritis, myocardial degeneration, degeneration of the muscle of the diaphragm, and, of special importance, neuritis and degeneration of nerves. To the last-named factors the involvement of the heart and diphtheritic paralysis are due. The general manifestations—the fever, prostration, visceral lesions, and neuritis—are caused by the

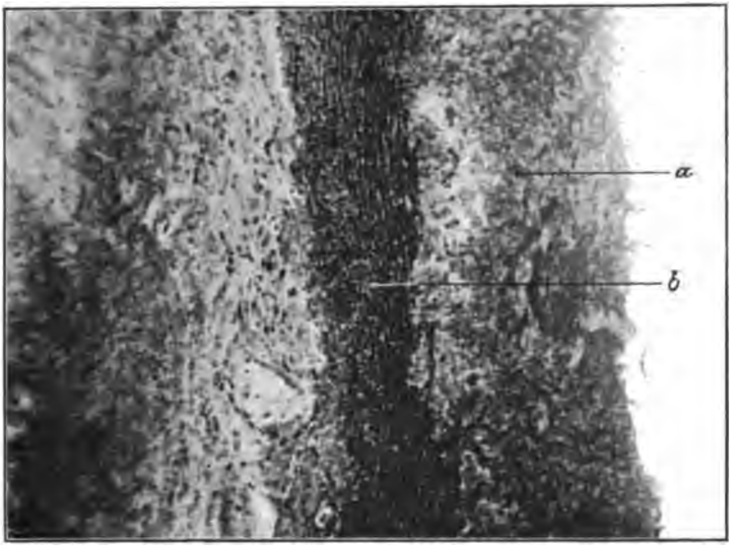

Fig. 8.—Diphtheria of pharynx. ***a*, The fibrinous exudation; *b*, the mucous membrane which has undergone coagulative necrosis. (Hæmatoxylin and eosin, × 125.)**

action of poisonous substances elaborated by the bacillus. These poisons, the *toxin*, are freely formed *in vitro* under artificial cultivation, and by successive injections of this toxin into horses the diphtheria antitoxin is prepared. The antitoxin will completely neutralise the toxin, and hence its use in treating the disease; but it cannot, of course, repair actual tissue damage, and early treatment therefore is of paramount importance. In cases treated with antitoxin on the first day of the disease the mortality is practically *nil*, but if treatment be delayed until after the third day, the mortality is but little less than with the old methods of treatment. The diphtheria of animals, birds, calves, etc., is a disease distinct from the human, but cats can probably contract human diphtheria and transmit the disease to man.

Various non-virulent bacilli, resembling in many particulars the diphtheria bacillus, are known, and have been termed "pseudo-diphtheria bacilli."

The bacteriological examination is of particular service in detecting mild cases and in pronouncing a case free from infection. As long as bacilli remain, *e. g.* in the throat, the case must be regarded as a possible source of infection. The bacilli usually disappear in two to three weeks, but occasionally persist for months.

TYPHOID OR ENTERIC FEVER is mainly contracted by infection by the digestive tract, generally through water, occasionally through milk, shell-fish, etc. Infection may also take place by the respiratory tract. The specific organism, the *B. typhosus*, is a short bacillus 2–4 μ in length, but shorter and longer, and large thread involution, forms occur in cultures. It is actively motile, possessing 8–12 flagella, non-sporing and non-Gram-staining. It forms a thick creamy growth on agar, a thin white growth without liquefaction on gelatin, a grey (almost invisible) growth on potato, and does not curdle milk. It forms acid but no gas from glucose, and does not attack lactose. It is agglutinated with typhoid serum. The bacillus is wide-spread in the body; it is found in the Peyer's patches and intestinal ulcers, in the mesenteric glands and spleen, scantily in the blood, in the rose spots of the eruption, in the sputum if there be pulmonary complications, and in the urine, particularly during convalescence. Catarrhal pneumonia and empyema, cholangitis and cystitis, and post-typhoidal suppuration (especially periosteal abscesses of the tibia and ribs) are caused by it.

The main lesion is met with in the bowel (Chapter XV), the spleen is enlarged and congested, focal necrosis occurs in the liver, the kidneys may be catarrhal, and in bad or long-standing cases degeneration of the myocardium and other muscles may be marked. The organism produces little or no toxin. A protective vaccine (Wright's) has been prepared with cultures. No complete theory has been propounded to account for the relapses which occur in this and some other diseases.

Para-typhoid fever is an infection which clinically resembles typhoid fever, but which is caused by a bacillus or group of bacilli belonging to the Gaertner group. These are like the typhoid bacillus morphologically, but produce both acid and gas from glucose. The true Gaertner bacillus (*B. enteritidis*) is an organism causing certain forms of epidemic meat poisoning. Another of the Gaertner group of bacilli produces an infective pneumonia among bird-dealers, etc. (Psittacosis).

The *Bacillus coli* (colon bacillus) is an inhabitant of the large intestine. It is a bacillus rather smaller than the typhoid, feebly motile, having 1–3 flagella, growing much like typhoid on agar and gelatin, but on potato producing a thickish straw-brown growth, curdling milk, and fermenting both glucose and lactose, with the production in each case of acid and gas.

It is capable of producing inflammation and suppuration, particularly in appendicitis and perforative peritonitis, ischio-rectal abscess, enteritis, cystitis, pyelitis and pyelonephritis, cholangitis, puerperal septicæmia, and, indirectly, is probably the cause of some of the cases of hepatic cirrhosis.

The *B. dysenteriæ* (dysentery bacillus) occurs in bacillary dysentery and in 60–70 per cent. of the cases of epidemic (summer) diarrhœa of infants. It is a small bacillus 2–3 μ in length, non-motile or very feebly so, in some of its cultural characters resembling the colon bacillus, but producing acid only and no gas from glucose, and not attacking lactose.

Anthrax is primarily a disease of cattle (splenic fever) but may be contracted by man either in a local form, the *malignant pustule*, or as a general septicæmia, *wool-sorters' disease*, usually from infected animals (butchers, veterinary surgeons, etc.) or from the hides or wool derived from infected animals (wool-sorters, porters carrying the bales, etc.). The malignant pustule is a cutaneous infection and is very common on the back of the neck (from the habit of carrying the bales on the back), on the face, and hands. It forms a large, dusky-red, inflammatory swelling, not unlike a carbuncle, and often covered or surrounded by little vesicles. It consists in an inflammatory leucocytic infiltration of the corium and papillæ, with sero-sanguineous exudation. In the septicæmic form, the infection is by the gastro-intestinal or respiratory tract, there is high fever, sanguineous diarrhœa, lobular pneumonia, sero-sanguinolent pleurisy, etc.

The anthrax bacillus, *B. anthracis*, is a large bacillus

5–10 μ in length with square-cut ends and forming in the body short filaments of half a dozen elements or so. It occurs in large numbers in the blood and organs, particularly the spleen. It stains well by Gram, is non-motile, and does not spore in the living body. It grows freely on agar, forming a creamy sticky growth which when young is finely granular like ground glass. It grows on gelatin, forming creamy masses with liquefaction. In a stab gelatin a very characteristic appearance is produced; it grows down the stab and from the puncture delicate fluffy outgrowths spread radially, so that the culture is much like an inverted fir-tree.

Under cultivation, the bacillus grows into segmented filaments of considerable length and spores freely, each segment producing a single, well-marked, ovoid, highly-resistant spore. It is the presence of these spores which renders wool, hides, etc., infective. Although the organism does not spore in the body, when the animal is skinned and cut up, the blood and tissues containing the bacilli are exposed to the air and free sporing takes place.

Tetanus.—This is an acute infective disease, generally resulting from the infection of wounds with material containing the tetanus bacillus, *B. tetani*. This organism, or its spores, is frequently present in the superficial layers of the soil, hence contused wounds soiled with earth are specially prone to develop tetanus. In the so-called idiopathic tetanus there has probably been some slight unnoticed wound or lesion which has become infected. No characteristic lesions are found in the disease.

The bacillus is a slender rod 4–5 μ in length, which forms a large resistant spore at one end, and the sporing bacillus thus resembles a drumstick. It is anaerobic and stains by Gram.

This organism forms an intensely poisonous extra-cellular toxin, the absorption of which gives rise to the tetanic symptoms, the bacillus itself being localised in the wound. This poison is absorbed by way of the *nerve-trunks* and not to any extent by the blood and lymph.

By injecting gradually increasing doses of the toxin into a horse a powerful antitoxin is generated.

BUBONIC PLAGUE is caused by a bacillus, the *B. pestis*, which is a shortish rod, 2–3 μ in length, with rounded ends, which have a marked tendency to deeper staining (polar staining). It is non-motile, does not spore, and does not stain by Gram. It forms a creamy, sticky growth on agar, a whitish growth on gelatin without liquefaction, and a flocculent, sticky deposit in broth, the broth remaining clear. In the bubonic form the bacillus is present in large numbers in the buboes, in the pneumonic form in the lungs and expectoration, and in the septicæmic form in the blood. All the varieties become septicæmic shortly before death. The organism belongs to the group of "hæmorrhagic septicæmic" bacilli, and the glands are infiltrated with a bloody serum and petechiæ occur in the skin and serous membranes.

MALTA FEVER, or Mediterranean fever, is caused by a non-Gram-staining coccus (*M. melitensis*). Clinically, it resembles typhoid somewhat, relapses are frequent, and joint pains often a prominent symptom; the spleen is enlarged and contains the organism. The disease is especially frequent on the Mediterranean littoral. The mode of infection is uncertain, but recently goats have been found to harbour the organism without showing symptoms and to excrete it in large quantities in their milk; infection is, therefore, very likely due to this source.[1]

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[1] See *Rep. of the Mediterranean Fever Com.* (Roy. Soc.) Pt. III, 1905.

Acute Rheumatism is being regarded more and more as an infective disease. Recently Poynton and Paine have isolated a small streptococcus-like form.[1]

Yellow fever was formerly believed to be due to a bacillus (*B. icteroides* of Sanarelli) belonging to the Gaertner group, but this is now known not to be the causative organism, which still remains to be discovered. The disease, *i. e.* the infecting agent, is, however, undoubtedly conveyed by a species of mosquito, the *Stegomyia fasciata,* under the following conditions: The mosquito must bite a patient during the first three days of the disease; an interval of some twelve to eighteen days then elapses before the insect becomes infective—probably some developmental cycle of the parasite taking place—and then for a few days, if the mosquito bites a susceptible person, infection occurs.

The principal lesions in this disease are fatty degeneration of the liver and kidney, hæmorrhagic nephritis, and hæmorrhages from the stomach and bowel.

Influenza.—A minute bacillus, difficult to cultivate, and not staining by Gram, is the cause of this disease. It is present in large numbers in the expectoration of the pulmonary complications. There are no specific lesions.

Relapsing fever.—A spirillar form is present in large numbers in the blood during the febrile paroxysms, but disappears during the apyrexial intervals. It is flexible and pointed at the ends, and is hence known as a spirochaeta (*S. Obermeieri*), and cannot be cultivated. Very probably it is a protozoon and not a bacterium, and may be a developmental stage in a trypanosome,[2] and be conveyed by some biting insect, very likely by the bed-bug. The spleen is very large in this disease, and anæmic infarcts and necrosis may be present in it.

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[1] See *Path. Soc. Trans.*, 1903 and 1904.

[2] Schaudinn has observed spirochaetes develop from a trypanosome in a bird. His observations, however, have not been confirmed by McNeal and Novy.

In *scarlatina,* a streptococcus has been described, also protozoa; in *soft chancre,* a small bacillus; in *measles,* various bacilli and protozoa; in *mumps,* micrococci and diplococci; in *whooping-cough,* bacilli; in *typhus,* bacilli, micrococci, and protozoa; and in *variola* and *vaccinia,* bacilli and protozoa. De Korté[1] has recently described an amœbiform protozoon in the two last-named diseases. In *hydrophobia,* which is contracted from the bite of a rabid animal, no organism has been detected with certainty. There are no gross specific lesions in the disease. In the medulla and spinal cord minute hæmorrhages occur, and collections of embryonic cells are present near the central canal—the rabic tubercles of Babes. In the sympathetic and cerebro-spinal ganglia, particularly of the pneumogastric, atrophy and shrinkage of the ganglion cells take place, so that the cells no longer fill their capsules, and their nuclei stain badly (Van Gehuchten).

It is not improbable that in some of the above-named diseases, the ætiology of which is uncertain, the parasitic organism may be ultra-microscopic, *i. e.* invisible with the best optical appliances at present available.

PROTOZOAN PARASITES.

The protozoa are minute unicellular animal organisms. They may be divided into the *sarkodina,* amœboid forms, the *flagellata,* the cells of which have one or a few long flagella, the *infusoria,* the cells of which are more or less covered with a number of short cilia, and the *sporozoa,* which are exclusively parasitic and have a complicated life cycle. To the *sarkodina* belongs the *Amœba coli* (*Entamœba histolytica,* Schaudinn), which is met with in certain forms of tropical dysentery in the contents of the bowel and in the tropical abscess of the liver, which is a sequel of this disease (see p. 363). The organism is a large cell 30–40 μ in diameter and consists of a clearer external zone or ectosarc and a more granular centre or endosarc, and bacteria, chromocytes, etc., are frequently present within this. The nucleus is seen with difficulty. Reproduction takes place by fission, and also by a form of encystment with sporulation.

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[1] *Lancet,* 1904, vol. ii, p. 1776.

Ciliated protozoa are not infrequent in the digestive tract as saprophytes, but only one species is pathogenic, the *Balantidium coli.* This is an organism not unlike the ordinary water *paramæcium,* occurs in certain forms of diarrhœa, and may cause a pseudo-dysentery. Flagellated protozoa may also occur in the digestive tract and elsewhere as saprophytes. One form (*Trichomonas vaginalis*) occurs in the vagina; it is a pyriform organism with three or four flagella and must not be mistaken for a spermatozoon; there is, however, no real resemblance between the two.

The TRYPANOSOMATA are an important group of parasitic flagellata. A trypanosome has an elongated spindle-shaped body, somewhat pointed at one end, prolonged into a single long flagellum at the other, and having a delicate undulating membrane on one aspect which starts from a small nuclear granule (micro-nucleus or blepharoplast) near the pointed extremity, and is prolonged into the flagellum. Near the centre of the body is a large or macro-nucleus. The trypanosomes live and are actively motile in the blood-plasma. One species (*T. Lewisi*) is common in the rat; another (*T. Brucei*) causes the tse-tse fly disease of horses in Africa; others cause various diseases in animals; and one species (*T. Gambiense*) is believed to be the cause of sleeping sickness of Central Africa.[1] The *T. Brucei* and *T. Gambiense* are conveyed by species of biting flies, the tse-tse flies (*Glossina morsitans* and *G. palpalis* respectively), in which a developmental cycle is probably passed. A flagellated protozoon, not unlike a trypanosome, also develops *in vitro* from the parasitic bodies (Leishman-Donovan bodies) met with in Kala-azar or tropical splenomegaly, a disease of India and other parts of the world. The Leishman-Donovan parasite is a minute spherical body containing a nuclear granule, and is found in the spleen (which is enormously enlarged) and bone-marrow.

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[1] In sleeping sickness the essential lesion is a meningo-encephalitis. A micrococcus not unlike the pneumococcus is almost invariably present in addition to the trypanosome in this disease, which is possibly due to a double infection with these two organisms.

COCCIDIOSIS is only exceptionally met with in man, but is common in the rabbit, the parasite being the *Coccidium cuniculi.*

MALARIA.—The parasite of malaria, first discovered by Laveran, is a protozoon belonging to the hæmosporidia of the sporozoa, and lives at the expense of the chromocytes of the host.

If the blood of a malarial patient is examined an hour or two before, or at the very commencement of, the febrile paroxysm, the parasite will be recognised as a pale, ill-defined mass of bioplasm within the red corpuscles, of which a variable proportion are infected, the size of the parasite varying in the different types of fever. When some hours old, a variable number of blackish pigment granules of melanin make their appearance. These subsequently coalesce into smaller groups, and the latter again into one or two larger, more or less centrally disposed, masses. The parasites exhibit more or less amœboid movement, and the melanin granules are frequently in a state of tremor. Later on, the parasite becomes divided into a variable number of segments, which separate and become spherical, the blood-corpuscle breaks down, the spherical bodies or spores are set free, and a certain number of them, again becoming attached to red corpuscles, develop into the first stage of the parasite. The melanin granules and some of the spores are ingested by phagocytes, and the melanin is deposited in the spleen and liver for a time.

The parasite, termed a *plasmodium,* or better, an *amœbula,* contains a nucleolus and a vesicular nucleus, and the melanin granules are present in the bioplasm surrounding this. When segmentation occurs, each segment contains a portion of both the nucleolus and the bioplasm. The maturation of each "brood" of parasites is coincident with a fresh paroxysm. In certain forms of malarial fever there exist in the blood for some time after the subsidence of the acute paroxysms well-marked, non-motile, crescentic, or sausage-shaped bodies, with rounded ends — the so-called "crescentic bodies" or "crescents"; their long diameter is greater ($\frac{4}{3}$) than that of a red corpuscle, their bioplasm is finely granular and contains at about the centre several well-marked pigment granules. In the crescentic forms the extremities of the crescent often appear to be joined by a delicate membrane; this is the remains of the blood-corpuscle in which the parasite has developed.

When fresh malarial blood is examined, it not infrequently happens that the so-called "flagellated bodies" make their appearance. These consist of a central bioplasmic mass, attached to which are from one to six delicate flagella measuring 20–30 μ in length. The flagella are actively motile and disturb the corpuscles, but the body itself does not move much. Frequently one or more of the flagella break away and swim free, remaining active for several hours. The flagellated bodies are never seen in the freshly-drawn blood, and Ross has found that flagellation does not occur if the finger be pricked through a spot of vaseline, the blood remaining covered with the film of grease. Careful observation has shown that they are developed from two distinct forms of the parasite, either from crescents, or from certain large round endo-corpuscular amœbulæ in the types of malaria in which the crescents are absent.

Various theories were held in the past as to the nature of these flagellated bodies. Manson suggested that the flagellated body constituted the first phase of an extra-corporeal existence, and formulated the theory that it was removed from the circulation by some blood-sucking insect, such as the mosquito. Through the brilliant researches of Ross, which have been confirmed and extended by observers in all parts of the world, this theory is now proved to be the correct one. The flagellated body represents the male cell or "male gametocyte," the flagella being analogous to the spermatozoa of higher animals. The female cells or female gametocytes are non-flagellated, and are fertilised by the entrance of one of the flagella of a male gametocyte. *This fertilisation takes place in the stomach* (middle intestine) *of certain species of mosquito,* and after fertilisation a series of changes ensues resulting in the formation of spore-like bodies, which are injected when the insect bites its victim, and thus the infection of fresh individuals with the malaria parasite takes place. The species of mosquitoes in which development takes place belong to the *anophelinæ.*

It is uncertain whether different species of parasites cause the different types of fever, but distinct differences may be made out in between the parasites of the benign quartan, benign tertian, and malignant types of malarial fever. The benign quartan and tertian parasites are of much the same size and ultimately invade almost the whole chromocyte, but the tertian is more actively amœboid and has finer pigment than the quartan. The malignant parasite is much smaller than the other two, and the crescentic bodies make their appearance in the plasma a week or two after the onset. In the malignant types of fever cerebral complications with coma may occur and are accompanied by massing of the parasites in the cerebral capillaries.

No toxin can be demonstrated in the blood of those suffering from a malarial attack, and it has been suggested that the fever is due to substances produced by the destruction of erythrocytes or leucocytes.

In malaria, pigment granules may be free in the blood or occur in the leucocytes and endothelium (*melanæmia*) and in the organs, particularly the spleen and liver. The spleen is enlarged, often markedly, and also the liver; both are hyperæmic and infiltrated with leucocytes in the earlier stages; later may become hard from fibrous hyperplasia.

METAZOAN PARASITES.

A number of animal forms belonging to the metazoa are parasitic in man and animals, and to these the term "parasite" is often restricted.

The principal parasites of this class are the various worms, and the lice, fleas, bug, and itch "insect."

The worms, or *vermes*, which occur in man belong to the (1) *Cestoda*, which are flattened and segmented, have no digestive tube, and are hermaphrodite; (2) *Trematoda*, which are not segmented, have an incomplete digestive tube, no anus, and are usually hermaphrodite; and (3) *Nematoda*, which are cylindrical worms having a complete digestive tube, and are not hermaphrodite. The lice and fleas and bug belong to the *insecta*. The lice are the *Pediculus capitis*, occurring on the hairy scalp; the *P. vestimentorum*, the body louse, infesting the underclothing; and the *P. pubis*, crab-louse, inhabiting the hairy parts of the body, particularly the pubes. They lay eggs, "nits," which may be seen as small ovoid greyish bodies attached to the hairs.

The bed-bug is the *Cimex lectuarius;* the common flea, *Pulex irritans;* the jigger, *P. penetrans*, met with in America and Africa, and burrows beneath the skin, especially of the feet. Other fleas occasionally occur. Certain flies (*œstrida*) occasionally lay their eggs in the nose, ear, or in wounds.

The itch insect, *scabies* (*Acarus scabiei*), is a mite and belongs to the arachnids. It is about the size of a small pin's head and burrows in the epidermal layer of the skin, causing much irritation. The *Pentastoma denticulatum* is also an arachnid, and in its larval state is met with in the internal organs, chiefly the liver.

The Cestoda, or Tape-Worms.

The tape-worms, which live in the intestinal tract, consist of a head from which flattened segments are continually being produced by gemmation, the segments near the head being therefore the youngest; each segment is termed a *proglottis.* Many of the segments (*proglottides*) contain the sexual organs and are hermaphrodite. The head is developed from a rounded embryo which passes its existence in the organs of an animal, the "intermediate host," and by migration passes to another animal, the "definitive host," in which sexual organs and maturity are attained.

The head, termed a *scolex,* is provided with suckers or hooklets, or both, and is continued into a narrow neck from which the proglottides develop. The mature proglottis is covered with a transparent cuticle within which is a muscular layer made up of longitudinal and circular bands. The male sexual organs consist of a testis, made up of convoluted tubes with vesicles. Minute vasa efferentia pass from these and unite at the middle of the proglottis into a common vas deferens, which terminates in a retractile copulatory organ, or *cirrhus*, opening with the vagina in a genital *cloaca*; this forms a projection on one margin of the proglottis which is known as the *genital pore* (Plate IX., A.). From this a vagina leads as a straight tube into an enlargement, the receptaculum seminis, from which an oviduct leads to the ovarian tube or tubes. The oviduct also receives a duct from a pair of yolk-bearing or vitelligenous glands, and passes into a simple, or, later, a branched uterus. The egg-germs leaving the ovary become impregnated with spermatozoa from the receptaculum, pass onwards, and become invested with yolk substance, and are then forced into the uterus, which, as it becomes distended with ova, may ultimately fill the whole segment (Plate IX., A.). The ova are thick-walled, the capsule being radially striated (Fig. 9, *d*). In each segment there is also a system of lateral tubes, the water vascular system, rudimentary nerves, and a parenchyma, in which calcareous granules are often present, which must not be mistaken for ova. Nutrition is carried on entirely by osmosis from the intestinal tract. As each proglottis matures it becomes detached, is to some extent motile, and may live and creep about for some time after separation discharging its eggs, which are passed in the stools. Should a suitable animal swallow the ova, they develop into the cystic or larval stage.

Tænia solium,[1] the common tape-worm in this coun-

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[1] The name "solium" is of uncertain origin. It is probably derived from a Syriac or other Oriental word meaning "chain."

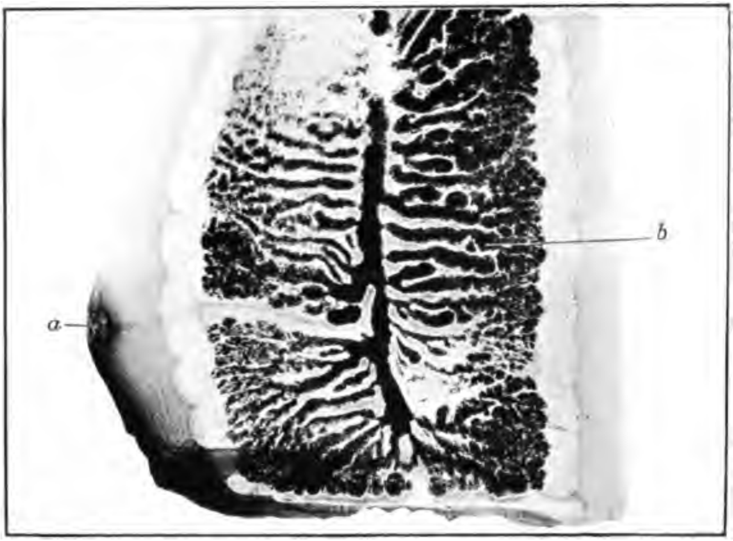
try, may be 2–3 metres in length. The head is the size of a pin's head and possesses four symmetrically placed rounded suckers, anterior to which is a ring of twenty-six hooklets mounted on a projecting portion, or rostellum. The neck is filiform, and measures 2–3 cm. in length. At first the segments are short, but about 130 cm. from the head they become mature, and each measures 9–10 mm. in length and 6–7 mm. in breadth. The genital pore lies at the side, somewhat behind the middle. The definitive host is man, the intermediate one the pig. The ovum having reached the stomach of the pig, the envelope is dissolved off and the embryo makes its way to one of the organs, where it becomes a cystic form, *Cysticercus cellulosæ*, known as a measle, and the flesh of an infected animal is termed "measly" (measly pork). Man is infected by eating the improperly cooked flesh. The *cysticercus* also occasionally occurs in man in the muscles, brain, etc.

Tænia saginata (*mediocanellata*) is larger than *T. solium* and may be as long as 4 metres. The head has four large suckers but neither hooklets nor rostellum (Plate IX., B.), and the segments are wider than in *T. solium.* The intermediate host is the ox, from eating the imperfectly cooked flesh of which man is infected.

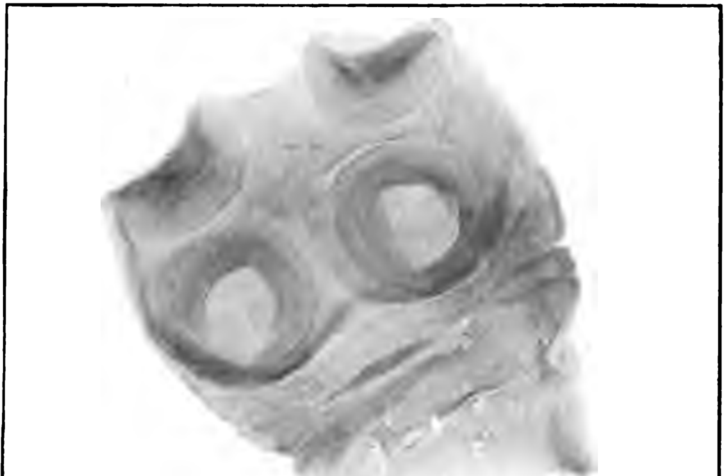
Dibothriocephalus latus (*Bothriocephalus latus*) is the largest of the human tape-worms, measuring 5–8 metres in length. The head is ovoid, 1 mm. long, and has two longitudinal slit-like suckers but no hooklets. The mature segments are two or three times as broad as long, and the genital pore is near the middle of the flat surface, not at the margin. It occurs principally in Switzerland and Eastern Europe, and the intermediate host is some fish.

Tænia echinococcus inhabits the intestine of the dog,

PLATE IX.



A. Segment or "proglottis" of a tape-worm. *a*. The genital pore. *b*. The uterus. (× 4.)



B. Head of a tape-worm, *T. saginata*. (× 20.)

To face page 146.

which is the definitive host; it is but 4 mm. in length and has only four segments, of which the last is as large as the rest of the body. The head has four suckers and a rostellum with 30–40 hooklets. Man is the intermediate host, and the development of the cystic form in the tissues and organs constitutes *hydatid disease*; in this large cysts are developed (*echinococcus cysts*), the commonest seat of which is the liver.

The wall of the *hydatid cyst* is formed of an external lamellar elastic cuticle, and an internal lining of parenchyma consisting of granular matter, muscle-fibres, etc. Around the cyst a certain amount of inflammation is set up, resulting in fibrous hyperplasia and the formation of a fibrous capsule. When the cyst has reached the size of a walnut it begins to develop secondary vesicles (brood capsules), which are formed by sacculated outgrowths from the wall of the capsule. When the rudimentary head has developed into a scolex it becomes retracted within the cyst, which it thereby invaginates. The head is minute, 0·3 mm. long, and has a rostellum with circle of hooklets and four suckers (Plate X., A.). The echinococcus cyst frequently remains single, and is filled with a clear watery fluid, containing no, or the merest trace of, proteid. The brood-capsules are always within it, and by detachment the hooklets may become free in the fluid and form an important diagnostic feature of the contents of an hydatid cyst. The cyst in some cases may rupture and cause secondary infection around, or occasionally suppurates. In some instances daughter-cysts are formed, or the cysts may be small and multiple.

The Trematoda, or Flukes.

The Trematodes are rarely met with in man outside the Tropics. *Fasciola* (*distoma*) *hepatica* is the cause of an important disease in sheep (fluke, or rot). A ciliated embryo escapes from the egg (Fig. 9, *e*) and passes into a fresh-water snail, where it undergoes a developmental cycle, escapes, and is eaten by the browsing sheep. It has been met with in man. *Paragonimus Westermannii* (*distoma pulmonale* v. *Ringeri*) occurs in the lungs in man in Japan and China, etc., and causes endemic hæmoptysis.

Schistosoma (*Bilharzia*) *hæmatobium,* which is bisexual, is a worm-like parasite, 10–20 mm. in length, and inhabits the portal vein and its mesenteric and splenic branches, and the visceral, uterine, and hæmorrhoidal veins. It causes endemic hæmaturia or bilharzia disease, which occurs in Egypt, West and South Africa, Mauritius, etc. The ova occur in the urine and are characteristic—ovoid, with a spine at one end, measuring 0·16 mm. in length (Fig. 9, *f*). They also occur in the rectum, where, however, the spine is *lateral,* and may cause papillomatous growths about the anus. If the urine containing the ova be diluted, a ciliated embryo escapes. It is believed that this passes into some water insect as an intermediate host.

The Nematoda, or Round Worms.

Several species are parasitic in man. *Filaria Bancrofti* (*Filaria sanguinis hominis, F. nocturna*) is the cause of the diseases elephantiasis, lymph-scrotum, chyluria, etc. In man the embryonic form mainly occurs. The worm is met with in the peripheral blood, *but only at night,* in the day-time retiring to the deeper vessels, particularly of the lungs. It measures about 0·3 mm. in length, and the diameter is about that of a red blood-corpuscle. It is enclosed in a delicate cuticle with granular contents, and is actively motile. Parental, *i. e.* sexual, forms are only occasionally met with, the two sexes living together in coiled masses in the lymph varices. The development of the embryo takes place in a mosquito (*Culex fatigans*). When the mosquito sucks the blood containing the filariæ, these shed their sheaths and make their way into the thoracic muscles, where a process of development takes place, and the metamorphosed filariæ ultimately find their way into the head, and after this are injected into the mosquito's next victim.[1] Generally the parasite is innocuous, but if for any reason it gets caught in the lymphatics, the various diseases mentioned may develop.

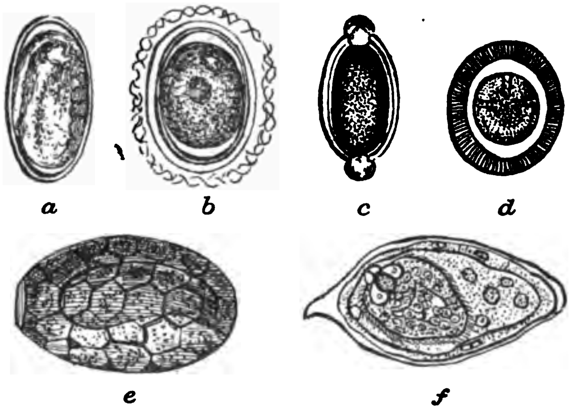


FIG. 9.—Ova of parasitic worms, etc. *a, oxyuris vermicularis; b, ascaris lumbricoides; c, trichocephalus dispar; d, tænia solium; e, fasciola hepatica; f, schistosoma hæmatobium.* (After Leuckart).

Ascaris lumbricoides, the large round worm, is not unlike an ordinary earth-worm in appearance and colour. The female is 20–30 cm. in length and 5–6 mm. in breadth; the male is considerably smaller—15–17 cm. long and 2–3 mm. broad—and its tail is bent up into a hook provided with two chitinous spines. The female genital orifice is a little anterior to the middle, and eggs are produced in enormous numbers, which at maturity are voided in the fæces. The egg is slightly ovoid, 50–60 μ in diameter, enclosed in a thick crinkled capsule, usually stained yellow by the fæces, which surrounds a thin, colourless, structureless, internal capsule, enclosing granular protoplasmic contents, which do not, as a rule, quite fill it (Fig. 9, *b*). Its life-history is not fully known. It is frequently met with and is found in any part of the intestinal tract, and occasionally may be vomited, or may pass into the bile-duct or gall-bladder, or into a hernial sac, or through an ulcer into the peritoneal cavity. Its presence, unless in large numbers or in an unusual situtaion, does not as a rule give rise to appreciable disturbance.

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[1] For further particulars see Manson's *Tropical Diseases*.

Oxyuris vermicularis, the thread-worm, is a small, whitish, cylindrical worm, the female 9–12 mm. in length, and tapering at the tail, the male 3–5 mm. long, blunt and curled at the tail, with a single spicule at the anus. The eggs are very numerous, distinctly ovoid, 50 × 25 μ in size, flattened on one surface, and enclosed within a thin transparent capsule, and generally containing a doubled-up, well-formed embryo (Fig. 9, *a*). It inhabits the lower ileum and upper colon, but migrates freely into the rectum and escapes at the anus, and may pass into the vagina. The eggs must be taken into the stomach before they can develop. They cause much irritation about the anus. (Common.)

Tricocephalus dispar, the whip-worm, is a common, but innocuous parasite of the cæcum and neighbourhood. Male and female are each 3–5 cm. in length, the anterior half of the body being thin and whip-like. The posterior end of the male is curled into a flat spiral, and has a single spicule. The eggs are ovoid, 50 μ in length, have a thick brownish capsule, with a peg-shaped perforated projection at either pole (Fig. 9, *c*). There is also a thin, uncoloured inner capsule, containing the granular contents. The first stage of the development of the egg seems to take place in water or moist earth.

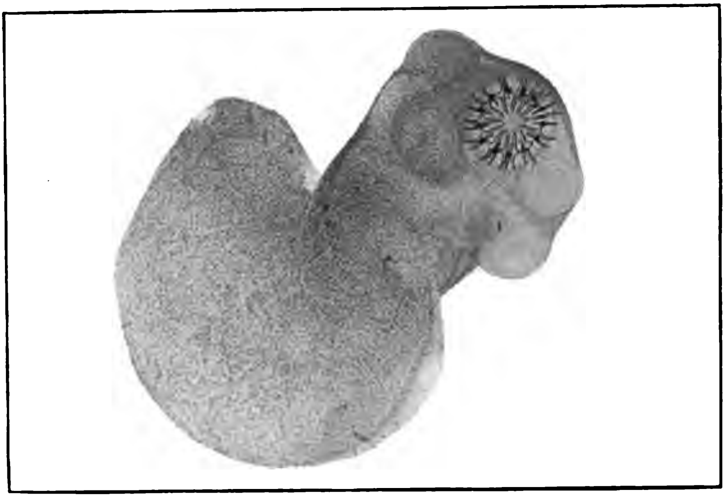
Uncinaria duodenalis (*ankylostomum duodenale*) is a parasite of considerable importance, causing the condition known as ankylostomiasis, the chief symptoms of which are progressive anæmia, digestive and bowel disturbance, and slight melæna. The blood-changes of severe anæmia are present, together with eosinophilia. The disease is widely distributed in tropical and subtropical countries, and has recently made its appearance in the Westphalian coal-mines and the Dalcoath tin-mine, Cornwall. The worms are whitish, and are found in the small intestine, to the mucous membrane of which they attach themselves and imbibe the blood, and may be very numerous. The adult females are 7–15 mm. long, the males slightly shorter. In each the mouth has two pairs of curved teeth posteriorly, and two triangular plates with sharp points anteriorly. The intestine commences as a muscular œsophagus, and is continued nearly straight to the anus, which is subterminal. The genital pore is slightly posterior to the middle of the body. In the male the caudal extremity is expanded into a membranous fold divided into four unequal lobes, and two long spicules can be protruded through the cloaca. The egg is ovoid, 50–70 μ long by 30–40 μ across, and is enclosed within a thin, transparent, uncoloured capsule. When the egg is passed it is usually segmented into four; but if the stool has stood, a larger number of segments will be present, and in twenty-four to forty-eight hours a well-formed embryo may be present in many of the eggs. Infection takes place either directly, by swallowing the eggs, or indirectly, through the skin, as has been shown by Loos. The larvæ, which develop in mud from the ova voided in the excreta, enter the body either by the mouth or through the skin, without perceptible lesion. From the skin they pass into the lymph- or blood-vessels, are swept into the general circulation, and eventually reach the lungs, whence they pass from the blood-vessels into the pulmonary alveoli. From the time the larvæ perforate the skin until they reach the lungs they remain the same size, but as soon as they reach the air-vesicles they begin to grow rapidly. They pass into the bronchioles, up the bronchi and trachea, and emerging through the glottis, pass down the œsophagus to the duodenum, where they become sexually mature.

Trichina spiralis causes the condition known as trichinosis, and is met with in two situations—the intestine and the muscles. The intestinal form, which is sexually mature, is a minute, whitish filiform worm—the female about 3 mm., the male 2 mm., in length. The alimentary canal commences as a muscular pharynx; widens into an œsophagus, which passes into a straight stomach and intestine opening at the posterior extremity. In the male, a tubular testis opens in the cloaca which is provided with two mammillary protuberances. In the female there is a simple ovary, uterus, and vagina, which opens at the genital pore at the junction of the first and second fourths of the body. The eggs develop in the uterus into embryos, which are born in the free state.

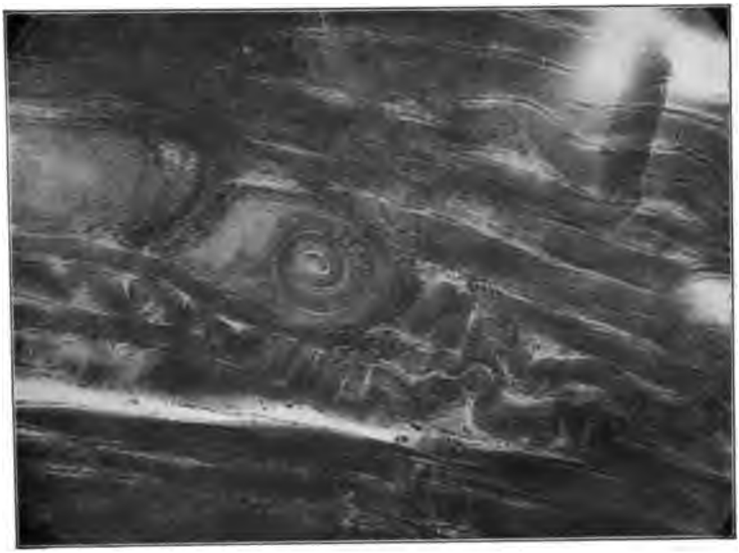
In the muscles the trichina is a small worm, 0·7–1·0 mm. in length, and is usually coiled up into a spiral enclosed in a fibrous capsule or cyst, which undergoes calcareous infiltration (Plate X., B.).

The life-history of the parasite is as follows: Man is usually infected by eating raw or imperfectly cooked

PLATE X.



A. A young echinococcus cyst. (× 30.)



B. *Trichina spiralis* in muscle. (× 100.)

To face page 152.

ham or pork containing the parasite. When the encysted trichinæ reach the stomach the capsule is dissolved off and the trichinæ are set free. They come to maturity in about two and a half days, pair, and the embryos begin to be produced about the seventh day and onwards. The embryos migrate from the intestine partly by passing directly through its wall, partly by the blood and lymph, seeking striated muscle. Once in the muscle, they penetrate the primitive bundles, the contents of which are reduced to mere detritus, and in a fortnight or so become mature. At first they are enclosed merely within the sarcolemma, but afterwards a cyst is formed partly of a chitinous secretion, partly of hyperplastic fibrous tissue, in the walls of which lime salts are deposited. The intestinal trichinæ live but a short time, five to seven weeks; but the muscle trichinæ retain their vitality for a much longer period, perhaps indefinitely.

The development of the trichinæ in the intestines is accompanied with fever, intestinal catarrh, and diarrhœa, and may simulate typhoid; in the muscles it is accompanied with fever, swelling, and œdema, and great pain, simulating rheumatism. The affection is frequently fatal. The parasite was first detected by Paget in 1834 and described by Owen.

The tape- and other worms cause pathogenic effects not only mechanically, by absorption of nutriment, and by abstraction of blood, but also by the production of toxic substances; these can be extracted from the bodies of tape-worms. In infection by the *Dibothriocephalus latus* and in ankylostomiasis blood-changes very nearly, if not quite, akin to those of pernicious anæmia may thus be produced.

CHAPTER VI.

FEVER AND PYREXIA.

"FEVER" and "pyrexia" are often used as interchangeable terms, but it is preferable to restrict the former to a complex of changes usually, but not necessarily, accompanied with a rise of body temperature, pyrexia being used to designate the elevated temperature of fever. Moreover, the phenomena which accompany the rise in temperature in a disease like enteric fever are very different from those that occur in certain cases of cerebral disease and injury, and the rise of temperature in the latter is preferably termed "hyperthermia."

The body temperature of higher vertebrates, mammals and birds, remains approximately constant irrespective of changes within limits of the surrounding medium, and these animals are therefore termed *homœothermic*, or *warm-blooded*; while in the lower vertebrates, reptiles, amphibians and fishes, and invertebrates it varies with the temperature of the surrounding medium, and these creatures are termed *poikilothermic*, or *cold-blooded*.

The normal body temperature (normothermia) differs in different animals, and in each animal varies within narrow limits under different conditions:

	Normal temperature.	**Variation in normal temperature.**
Man	37·0° C. (98·6° F.)	36·2°—37·8° C.
Monkey	38·1° C. (100·6° F.)	36·9°—39·7° C.
Horse	37·8° C. (100·0° F.)	36·1°—38·6° C.

	Normal temperature.	Variation in normal temperature.
Dog	39·0° C. (102·2° F.)	37·1°—39·9° C.
Rabbit	39·5° C. (103·1° F.)	37·9°—40·8° C.
Guinea-pig	39·1° C. (102·4° F.)	37·0°—39·2° C.
Hen .	42·2° C. (108·0° F.)	

In man there is a normal diurnal variation, the temperature being highest in the evening between 5 p.m. and 7 p.m. and lowest in the early morning between 3 a.m. and 6 a.m., the extreme range being about 1–1·5° C. This diurnal variation probably largely depends on activity and feeding; for reversal of the natural mode of life, making the day the period of rest and the night the period of activity, tends to invert the temperature curve, but not altogether, for in the hypnotised fasting individual the normal diurnal variation still continues to a slight extent.

Obviously the constancy of the temperature of homœothermic animals must depend on a delicate balance and adjustment between heat-production (thermogenesis) and heat loss (thermolysis).

Thermogenesis is caused by destructive metabolism (katabolism) in the body, the oxidation of material in the tissues. The chief seat of these changes is in the muscles, and the main source of heat production is therefore muscular contraction, not only of the skeletal muscles, but also of the heart, respiratory and intestinal muscular tissue. Excitation of the spinal cord in an animal, with production of tetanic contractions of all the limbs, may cause a rise of temperature up to 44° C. The next important source of heat is the liver, and the temperature of the hepatic vein is higher than in any other place in the body. The activity of the brain and glands and chemical changes in the digestive tract may also contribute something, but a very small amount, to thermogenesis; the heat production by the glands (salivary) is not measurable. The *final* disintegration of the foodstuffs takes place in the tissues, and when it is stated that oxidation of food is the source of heat it must be understood that not only digestive-tract changes but also tissue metabolism are included.

Various foodstuffs have different *heat values* as they are termed, which are estimated in *kilocalories*.[1] According to Rubner the complete combustion of—

1 gram of proteid yields 4·1 kilocal. (gross) and 3·2 kilocal. (net).
1 gram of fat yields 9·3 kilocal. (gross) and 8·4 kilocal. (net).
1 gram of carbohydrate yields 4·1 kilocal. (gross) and 3·8 kilocal. (net).

The gross amount is that yielded by the *complete* combustion of the substance, except in the case of proteid from which the heat-values of the urea, uric acid, and ammonia have been deducted, since in the body proteid is not completely oxidised (the total heat value of 1 gram of proteid is 5·5 kilocal.). The net value is that which is believed to be produced physiologically, deductions being made for non-absorption, etc. From these data the heat values of any diet may be calculated.

Thus, taking the following as a diet on which a man may be maintained in health, neither gaining nor losing weight, the heat value works out as follows:

Proteids .	100 grams	= 100 × 3·2 =	320 kilocal.
Fats . .	100 „	= 100 × 8·4 =	840 „
Carbohydrates	240 „	= 240 × 3·8 =	912 „

Total net heat value of such a diet = 2072 „

It is to be noted that the heat produced under ordinary circumstances would, if accumulated, be sufficient considerably to increase the body temperature were there not heat loss going on at the same time.

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[1] A "calorie" is the amount of heat required to raise the temperature of 1 gram of water 1° C. (*e. g.* from 0° to 1° C.). A "kilocalorie" is one thousand times this amount.

Thermolysis.—The chief seat of heat loss is the skin, to a small extent by conduction and radiation, but mainly by evaporation of the sweat. The conversion of water into vapour is accompanied by an enormous disappearance of heat, the heat used up in converting one gram of water at 100° C. into steam at the same temperature amounting to no less than 536 calories. The heat lost by the skin amounts to about 77 per cent. of the total loss. The lungs are the next most important seats of heat loss, partly by warming the inspired air, when the temperature is lower than that of the body, and partly by evaporation, the expired air being saturated with moisture. This source of loss constitutes about 20 per cent. of the total. The remaining 3 per cent. is used up in warming the food and drink when taken into the body, though this heat is not actually lost until the warm urine and fæces leave the body.

Thermotaxis, or *heat regulation,* is normally carried out by variations in thermogenesis and thermolysis. When the external temperature is high, thermogenesis tends to be diminished by a disinclination for muscular effort, and disinclination for food, especially fats. At the same time thermolysis is increased by quickened heart's action and dilatation of the cutaneous vessels, whereby more blood reaches the skin, and more heat is therefore lost by conduction, by radiation, and by evaporation, since the sweat-glands secrete more profusely, also by quickened respiration, and man naturally inclines to clothe himself less warmly. If the external temperature be low, thermogenesis is increased by an inclination for more food, especially fats, and for more muscular exertion. At the same time thermolysis is diminished by contraction of the cutaneous vessels and by a lessened secretion of sweat, and warm clothing is adopted by man. Shivering may be a natural means whereby heat-production is increased through muscular action.

But how are these factors of heat production and heat loss co-ordinated so that an almost perfect balance between the two is maintained, and the normothermia remains practically constant? Undoubtedly through the nervous system, partly by means of the vaso-motor nerves controlling the blood-vessels, which are probably stimulated reflexly from the surface, and partly, perhaps, by means of regulating cerebral heat centres, though these have not yet actually been demonstrated. The existence of the latter is rendered probable by the effect of pricking the anterior part of the corpus striatum, which is followed by pyrexia, with increased elimination of carbon dioxide, as are also injuries, natural or experimental, of the pons and of the cortex in the neighbourhood of the cruciate fissure. The efferent nerves cannot be differentiated from the motor and vaso-motor ones, nor the afferent ones from those of ordinary sensation.

Pyrexia and Hyperthermia.

As already stated, "fever" and "pyrexia" are often used as synonymous and interchangeable terms. It is preferable, however, to regard *fever* as the group of phenomena comprising (*a*) rise of temperature (usually), (*b*) cardiac and respiratory acceleration, (*c*) altered metabolism, and (*d*) functional and structural alterations such as are commonly seen in diseases like enteric and other continued fevers, and *pyrexia* as signifying the rise of temperature which occurs in fever.

PYREXIA usually accompanies fever and inflammation. It is not, however, an absolutely essential part of fever, and is occasionally, though rarely, absent.

HYPERTHERMIA is a rise of temperature which is not accompanied by the phenomena of fever. It may be caused by:

(1) Excessive muscular exertion, which may be followed by a slight rise of temperature.

(2) An excessive external temperature, and in this respect a moist medium is much more effective than a dry one. In dry air a man may remain for some time (half an hour) exposed to a temperature of 60°, 70° or even 80° C. without much change in the body temperature; while a warm or vapour bath of 45° C. quickly causes a hyperthermia, or rise of temperature. The reason for this difference is obvious. In the one case, evaporation from the surface is free and thermolysis active; in the other, evaporation is restricted and thermolysis correspondingly diminished.

(3) Heat-stroke (insolation) or heat-apoplexy occurring in hot weather, and particularly in certain parts of the Tropics, is accompanied by hyperthermia, and is probably caused partly by the high external temperature, but partly also perhaps by diminished excretion, whereby waste products accumulate and cause a toxæmia. Heat-stroke is to be distinguished from heat-exhaustion, which is virtually syncope. Heat-stroke, sun-traumatism, or siriasis, is geographically restricted, occurring solely in the Tropics in certain low-lying coast districts and river valleys. (Manson). Sambon has asserted that it is a germ disease. By some it is considered to be due to the chemical, rather than to the heat, rays.

(4) Urethral or catheter fever, produced by the passage of a catheter, may also be classed as hyperthermia, possibly due to reflex disturbance of the thermotaxic cerebral centres. Extraordinarily high temperatures have also been recorded in cases of hysteria.

(5) Many cerebral injuries and apoplexy, especially of the pons and corpus striatum, are followed by hyper-

thermia, which may be unilateral and on the side opposite to the lesion. Such disturbance of temperature does not usually last more than two or three days, and has been regarded as being produced by alteration in the centres controlling metabolism, with increased thermogenesis therefrom. Tumours or injuries of the cervical spinal cord may also be accompanied with marked hyperthermia.

(6) In aseptic trauma, *e. g.* simple fracture of a bone, leukæmia, tumour-formation, and certain other conditions hyperthermia may occur. The cause is uncertain; possibly the substances derived from broken-down leucocytes or other cells are pyrogenetic.

(7) Lastly, certain drugs cause hyperthermia—cocaine, strychnine, belladonna, and β-tetrahydronaphthylamine. The latter is considered by Hale White to induce rise of temperature by increasing thermogenesis.

In the young animal thermotaxis is unstable, and in infants and young children very slight causes may induce marked rise of temperature. Pembrey and Gordon have shown that the embryo chicken is practically poikilothermic.

HYPOTHERMIA or subnormal temperature, the antithesis of hyperthermia, may conveniently be considered here. The causes of this condition are: (1) lowered external temperature. The normal body temperature of a naked man cannot be maintained if the external temperature fall below about 27° C. The lowest body temperature that may be survived is uncertain, but cases are on record in which the rectal temperature has fallen to 30°–25° C. as a result of exposure, and the individual has been resuscitated; (2) starvation; (3) chronic diseases, such as nephritis, myxœdema, anæmia, malignant disease, and particularly chronic pulmonary (*e. g.* emphysema) and cardiac diseases; (4) as a sequel of fever.

Frequently after an acute specific fever, enteric, for example, the body temperature may for a time during convalescence be subnormal; (5) lastly, shock and collapse are associated with marked fall of temperature.

Antipyretic drugs such as antipyrin and quinine also lower the temperature if there be pyrexia. Quinine diminishes nitrogenous metabolism and may thus tend to diminish thermogenesis. Its action in malaria is, however, to destroy the parasite and so bring the febrile process to an end. Antipyrin similarly reduces nitrogenous metabolism and, in addition, seems to influence the central mechanism presiding over thermolysis, for the volume of the limb of a febrile patient increases on its administration. Alcohol tends to lower temperature by stimulating the circulation, dilating the cutaneous vessels, and increasing thermolysis; it also diminishes metabolism.

CAUSES OF FEVER.—Fever, as here defined, is almost always caused by the action of certain substances which may be termed pyrogenetic, and which are products of infective agents—bacteria, protozoa, and other parasitic organisms. The pyrogenetic substances seem to be generally proteid in nature, bacterial proteids, ferments, and proteoses. The alkaloidal substances, which may also be formed by micro-organisms, seem generally to be non-pyrogenetic.

Stages, Degrees, and Types of Fever.

STAGES OF FEVER.—Most fevers are divisible into three stages: (1) the initial or cold stage—stage of invasion, when the temperature is rising; (2) the fastigium or hot stage, when the temperature has attained and remains at a more or less constant level above normal, and (3) the terminal stage, the stage of decline or defervescence, when the temperature is falling.

The *initial stage* may be gradual in onset, as in enteric, or sudden as in malaria and pneumonia. With sudden onset there is usually a marked rigor, the patient feels cold and chilly, the surface is pale or blue and cold, and he shivers. Although the skin is cold and the surface temperature is subnormal, the internal temperature is rising. This stage does not last long, at the most not more than a few hours, passing into the second stage. When the onset is gradual some chilliness or even slight rigors may be experienced, but they are hardly ever so pronounced as when it is sudden. The temperature may take five or six days to attain its acme in enteric.

The *second stage*, or fastigium, may last from a few hours to days, weeks, or months. When the temperature reaches its acme the sensation of chilliness passes off, the cutaneous vessels dilate, and the surface becomes flushed, hot, and dry. Heat and dryness of the surface are particularly met with in acute pneumonia, scarlatina, and measles. In some instances there may be sweating, which may be profuse, as in acute rheumatism, during this stage. The temperature then remains at a fairly constant mean level, with sometimes considerable fluctuations and diurnal variation.

The *terminal stage* may occupy several days (termination by "lysis"), indicated first by greater excursions of the diurnal variation and then by a gradual decline day by day, as in enteric, or it may be of brief duration with rapid fall in the temperature, which may attain the normal in a few hours (termination by "crisis"), as in malaria and acute pneumonia. Termination by crisis is often accompanied by profuse sweating, a large excretion of urine, and acceleration of respiration.

DEGREES OF FEVER.—When the temperature does not rise above 37·8° C. (100° F.) the fever is said to be *slight*, between 37·8° and 39·4° C. (100°–103° F.) it is *moderate,* between 39·4° and 40·5° C. (103°–105° F.) it is *high,* while over 40·5° C. or thereabouts (105°–105·5° F.) it is regarded as *hyperpyrexia.*

It is to be noted that there is also a *febris sine febre,* fever without pyrexia, the temperature being only slightly or not at all above normal, yet the other phenomena of fever being present. This is occasionally seen in diphtheria, septicæmia, and typhus, rarely in enteric and other fevers. It is generally a serious condition, accompanied with profound prostration, coma, muttering delirium, etc. It is to be distinguished from the intercurrence of some untoward event with depression of temperature—such, for example, as perforation in enteric, in which the shock of the perforation causes a fall of temperature, which may more than counterbalance the rise due to the febrile process, and actually determine a subnormal temperature for a time.

TYPES OF FEVER.—When the pyrexia is maintained at about the same level, allowing for the diurnal variations, never touching the normal, the fever is said to be *continuous,* as in most of the specific fevers. If there be diurnal variations of more than 1° C. (2° F.), the temperature still never falling to normal, the fever is said to be remittent. In the *hectic* and *intermittent* types the temperature falls to normal every day; an excursion of 2°–3° C. may thus result.

In certain instances relapses occur, the temperature falls to normal, and for a few days the patient may seem to be convalescent, then pyrexia again ensues and the febrile process is repeated. This is typically seen in relapsing and enteric fevers.

Changes in Fever.

The *circulation* is affected in fever, as is shown by the accelerated pulse rate, the acceleration averaging 8 pulsations for every degree Centigrade (= 4½ for 1° F.). The acceleration of the heart is due, not only to the action of the heated blood and pyrogenetic substances on the cardiac centres, but also to a direct action on the cardiac muscles (and intrinsic nerves?), as has been shown by perfusion experiments on the isolated mammalian heart. The blood-pressure is usually raised during the initial stages, as is shown by the full bounding pulse, but is nearly always reduced in the later stages, due to a combination of cardiac weakness and lessened arterial tension. There are exceptions to the rule that the heart is accelerated in fever; *e. g.* in basal meningitis there is frequently retardation, due probably to stimulation of the vagi.

The *respiration* is accelerated, but the pulse-respiration ratio usually remains about the same as in health, unless pulmonary complications or affections of the cardiac muscle, *e. g.* myocarditis, ensue. The respiratory acceleration is similarly due to action on the respiratory centres, for even in acute pneumonia the respiratory frequency decreases at the crisis, though the consolidation and impairment of the lung must, for a time, be unaffected.

The *secretions* are profoundly modified. All are more or less diminished—saliva, sweat, gastric and pancreatic juices, bile, and urine. The urine is concentrated, dark in colour, and of high specific gravity, and deposits urates. Not infrequently albumin (febrile albuminuria), sometimes proteoses, and other abnormal substances are present, aceto-acetic acid, β-oxybutyric acid, lactic and volatile fatty acids, acetone (present in the merest traces in health), pathological urobilin, and the substance giving the diazo reaction. The excretion of sodium salts and of chlorides is diminished (principally, apparently, because they are scanty in the fever patient's diet), especially in acute pneumonia, in which the latter may completely disappear, while that of phosphates and of potassium salts may be increased.

Cerebral activity is often increased in the earlier stages, but later becomes dull or perverted, and delirium and hallucinations may occur. The volume of the blood is frequently diminished (oligæmia), also the number of chromocytes (oligo-cythæmia), while the alkalinity is usually decreased, though occasionally increased.

Metabolism in Fever.

The respiratory exchange.—The ratio, or proportion, between the output of carbon dioxide and the intake of oxygen $\left(\frac{\text{Vol. of } CO_2 \text{ excreted}}{\text{Vol. of } O_2 \text{ absorbed}}\right)$ is a relatively constant quantity, which is known as the "respiratory quotient," and is a measure of the respiratory exchange. It varies with the diet—for an ordinary mixed diet being 0·85. Usually, in fever the respiratory quotient remains unaltered from that obtaining in a normal individual under the same conditions and diet, though in the initial stages both the intake of oxygen and the output of carbon dioxide are increased, while in the later stages both are diminished.

The discharge of nitrogen is decidedly increased in the febrile stage—urea, uric acid, kreatinin, xanthin bodies, and ammonium salts all being present in the urine in quantity larger than normal. Since these nitrogenous bodies are largely derived from proteids, the disintegration of proteid must be increased in fever. Urea is regarded as being derived from proteid; uric acid and its allies—xanthin, hypoxanthin, etc.—are regarded as being derived from nucleo-proteid, and therefore nucleo-proteid, as well as proteid, is disintegrated in the febrile process, and is probably derived from the nuclei of the leucocytes and other cells.

The STRUCTURAL CHANGES in fever are wasting, not only of fat, but also of proteid, cloudy swelling and fatty degeneration of epithelium, particularly of the kidney and liver, and of muscle, especially cardiac and respiratory, and Zenker's degeneration of the former. These changes are not altogether dependent on the pyrexia, for they may be very marked when the temperature is not high, and are therefore also due to the action of the pyrogenetic substances. Rabbits kept at a temperature of 41° C. for a week show a moderate amount of cloudy swelling and fatty degeneration (Welch). In ordinary fever, both the pyrexia and the pyrogenetic substances are therefore responsible for these structural changes. The tongue is also profoundly affected, the liver loses its glycogen and sugar, and the body fat disappears. The ganglion cells of the brain and cord may show swelling, vacuolation, and chromatolysis.

In cases of hyperpyrexia the ganglion cells of the whole central nervous system, on staining with methylene blue, stain diffusely and homogeneously, the Nissl granules have disappeared, and the stainable substance has a fine, dust-like appearance.

Theories of Fever.

Granting, as we must do from what has previously been stated, that there is a fever-producing substance, the manner in which this acts in causing a rise of temperature, with accompanying changes in metabolism, is still very obscure. Most pathologists believe that the fever-producing substance disturbs the balance of the cerebral centres presiding over thermotaxis, and that the disorders of metabolism are secondary to this. Some, however, have held that the fever-producing substance directly attacks the tissues.

Accepting the first view, viz. that the fever-producing substance deranges thermotaxis, the *cause* of the rise of temperature is much disputed. There are three principal theories :

(1) That of **Liebermeister** suggests that the thermotaxic mechanism behaves approximately as in health, but is, as it were, "set" for a higher temperature. Thus, in the febrile condition the same diurnal variation in the temperature curve occurs as in health, and if the febrile patient be cooled he shivers, and if he be warmed he sweats, just as a normal individual would under the same alterations of temperature (0·2–0·5° C. *below* or *above* the mean in both cases). But, as Lazarus-Barlow points out, these phenomena merely show that the fevered individual behaves more or less like a normal individual when the temperature is falling or rising, and do not prove that his thermotaxic mechanism is "set" for a higher temperature in the sense that a thermo-regulator may be so set.

The diurnal variations of temperature in fever often show far greater excursions than in health, and, as was pointed out by Cohnheim, profuse sweating in fever caused by an injection of pilocarpine does not lower the temperature, though heat-loss must be enormously increased. These facts are opposed to the theory of a higher "setting" of the mean temperature as being the cause of the pyrexia in fever.

The temperature, moreover, is much more mobile in fever than in health. Thus, a healthy man may remain in a bath at 25° C. (77° F.) for three hours with a reduction in his temperature of but 0·6° C. (1° F.), and in a bath at 15° C. (59° F.) with a fall of 1° C. in the same time. The temperature of a fevered patient, on the other hand, is rapidly reduced by a tepid bath—a bath at 20° C. will usually cause a drop of 1° C. in fifteen or twenty minutes.

(2) TRAUBE'S THEORY asserts that the *quantity* of heat generated during fever is approximately the same as in health, but that heat loss is diminished owing to disturbance of the thermolytic centres that preside over heat loss. The initial stage of fever is often ushered in with a rigor, in which condition the cutaneous vessels are contracted and the skin is cold and dry, a fact supporting this theory. During the fastigium heat-loss is stated to be diminished owing to a lessened secretion of sweat. But the skin in fever, though often dry, is by no means always so, *e. g.* in acute rheumatism in which profuse sweating occurs. Nevertheless, the normal vascular response to stimulation of the skin is undoubtedly altered. Heidenhain found that in fever reflex stimulation of the vaso-motor centres does not increase the cutaneous circulation, as is the case in the normal animal, and Burdon-Sanderson directs attention to the fact that if a pencil be drawn firmly over the skin, particularly in typhoid, the track after a few seconds becomes relatively pale. Other facts support this theory. Maragliano has found that the volume of a limb is decreased during a rigor in malaria, presumably owing to contraction of the vessels, especially of the skin, and diminution in the amount of blood, and that this decrease in volume precedes the rise in temperature.

It is probable, however, that thermogenesis is generally disturbed in fever. In the initial stage it is often increased, and may be throughout.

(3) MACALISTER'S THEORY.—MacAlister assumes that heat regulation is carried out by the interaction of three centres—a thermolytic centre, a thermogenetic centre,

and a thermotaxic or regulating centre co-ordinating and controlling the other two; and he regards disturbance of the thermal relations of the body as being brought about as follows: "First and most easily disturbed is the thermotaxic nervous mechanism. If that is all that is disturbed, we shall have strange risings and fallings of temperature as the independent variations of production and loss are concurrent or the reverse, but there need be no fever. The balanced rhythm of anabolism and katabolism in the muscles is not disturbed; there is no excessive oxidation and no excessive inhibition. And the balanced rhythm of the respiration and the cutaneous circulation is also maintained, and with it the process of heat-loss, but the latter need never be very excessive or very deficient. All that happens is that the two rhythms do not harmonise, and the fluctuations of the temperature correspond in a measure to the 'beats' which are heard when two tones are sounded together that are nearly but not quite in concord.

"This condition is one of 'thermal ataxia,' and is seen in catheter fever, hysteria, and cerebral pyrexia. The next degree of disturbance is that in which there is not only thermal ataxia, but disorder of the parts of the nervous system subserving heat-production; there is under-action of the anabolic nerves, with diminished construction and diminished absorption of energy; there is over-action of the katabolic nerves, with increased oxidation and thermogenesis. Both factors of the normal thermogenic tonus are probably disordered together, but as I believe there is good reason for regarding the anabolic mechanism as 'higher' than the katabolic, so there is reason for the view that it is in many cases the first and the most disordered. Weakening, or abolition of the inhibitory influences, with defective upbuilding of the 'thermogenic stuff' in the muscles probably precedes excessive katabolic action, and to this may be due the prefebrile discharge of urea which is occasionally observed. But soon the other factor of the thermogenic mechanism is disordered also, and there is excessive heat-production. The net result is apparent wasting, or 'combustion,' and generally high temperature. The thermotaxic mechanism is in abeyance; the immediate adjustment of heat-loss to heat-production is consequently hindered; the thermogenic mechanism gets a start, as it were, before the heat-discharging mechanism is called into play. Once the temperature is somewhat raised, the latter mechanism, if it is not itself disordered, is capable of increased activity, and presently overtakes the work thrown upon it. But the 'lagging' of the one process behind the other finds expression in the heightened temperature. This is ordinary pyrexia, and the nervous disorder does not in general go farther.

"But there is another stage — namely, when the mechanism of heat loss is also profoundly disordered, so that the rise of temperature from the antecedent excessive thermogenesis does not stimulate it (or does not stimulate it enough) to make it overtake the latter until the temperature reaches an excessive or even a fatal height. This is hyperpyrexia.

"To sum up. The thermal nervous system has three parts; let us call them briefly the thermotaxic or adjusting, the thermogenic or producing, and the thermolytic or discharging mechanism. Disorder of the first implies irregularities of temperature only; disorder of the first and second implies, in general, heightened temperature and increased body heat—that is, ordinary fever; disorder of the first, second, and third implies, in general, hyperpyrexia, dangerous increase of heat, and steadily *rising* temperature."

With regard to MacAlister's theory, Burdon-Sanderson points out that "in a warm-blooded animal of constant temperature the supply of heat is always potentially in excess. It is obvious that in a warm room more heat is produced than is wanted, but not so obvious, though equally true, that in the cold of winter the body temperature would rise at any moment if surface loss were suspended or annulled. In the two cases the 'mechanism' is the same. It, therefore, does not seem necessary to imagine more than one regulating centre *in constant operation*—that which presides over surface loss."

On the whole, the balance of evidence is in favour of Traube's theory, with some modification, viz. that it is the function of thermolysis that is chiefly disturbed in fever, thermogenesis in some instances being approximately normal, but usually slightly increased.

Hyperpyrexia.—The great danger of hyperpyrexia has been ascribed to various causes. It might be thought that it is due to a large excess of the pyrogenetic substance causing intense toxæmia, of which the high pyrexia is a sign. This may be partially true, but the fact that reduction of the temperature by artificial means, *e. g.* the cold bath, to a large extent removes the danger shows that this is not the whole explanation.

Mott and Halliburton[1] have advanced a physico-chemical theory which is supported by the results of experiment. In a research on hyperthermia on animals, Marinesco has pointed out that a temperature of 47° C. is immediately fatal, one of 45° C. kills in one or two hours, and one of 43° C. after a longer interval. In nearly all organs and tissues there is a globulin present which Halliburton has shown coagulates between 45° and 50° C. By heating solutions of neuro-globulin for some hours to 42° C., flocculi of coagulated proteid were observed to form, while a temperature below this, maintained for eight hours, produced no coagulation. If the brains of rabbits and cats were heated to 42° to 43° C. for 3½ hours and then extracted with saline solution, it was found that the saline extract contained only about half the amount of proteid compared with the extract of an unheated brain, and that it gave no coagulation flocculi when heated to 47° C. Mott and Halliburton conclude, therefore, that the physico-chemical cause of death from hyperpyrexia is due to the coagulation of cell-globulin. When this constituent of cell-protoplasm is coagulated the protoplasm as such is destroyed. The temperature at which such coagulation is most easily produced is 47° C. But temperatures as low as 42° C. will have the same effect, provided the heating be continued long enough.

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[1] *Archives of Neurology*, vol. ii, 1903.

The Use of Fever.

The question has been raised as to whether fever may not be beneficial to the economy. Within limits it may be so; the physician would generally prefer to see a moderate degree of pyrexia (102°–103° F.) in a disease like enteric fever, rather than a slight one, which is often accompanied by serious symptoms, prostration, coma, and delirium. Experimentally, it has been found that animals rendered hyperthermic by cerebral puncture and infected with the pneumococcus live longer than control animals, and that rabbits similarly infected live longer if kept in a warm chamber (41°–42° C.), than control animals at room temperature. Birds which normally have a high temperature are resistant to anthrax, but may be infected after chilling.

CHAPTER VII.

ŒDEMA AND DROPSY.

THE tissues are bathed in a fluid, the lymph, which is a transudation from the vessels mixed with the products of tissue change. This fluid is normally reabsorbed by the lymphatic vessels and returned to the venous system *viâ* the thoracic duct. Certain changes in the circulatory system may lead to an increased transudation, which, however, up to a certain point may be compensated by increased absorption. But this compensation has its limits, and if the transudation still goes on a time comes when the saturation of the tissues rises above the normal, fluid collects in the tissues, organs, and cavities of the body and the condition known as dropsy results. Dropsy of the cutaneous tissues is termed œdema or anasarca, of solid organs, œdema, of serous cavities, hydrops or dropsy. Dropsy of the lateral ventricles of the brain is hydrocephalus; of the pericardium, hydropericardium; of the pleural cavity, hydrothorax; of the peritoneal cavity, ascites; of the tunica vaginalis, hydrocele. Tissues which are the seat of œdema are swollen, the degree of swelling depending on the looseness of texture of the part, are soft and doughy in consistence, and leave a pit on pressure which persists for some time. The cutaneous tissues and serous cavities are capable of considerable distension; the solid organs are not so distensible. Structures and organs in serous cavities may be compressed by the accumulation of fluid. Cut into, dropsical tissues are usually pale, glistening, and sodden in appearance, and contain less blood than normal, and more or less serous fluid trickles away. The kidneys and liver do not retain much excess of fluid, but the lungs can hold a considerable quantity, which on pressure flows out as a frothy fluid.

Microscopically, the fibrous bundles of the tissues are separated, the fibrillæ and cells are swollen, and the outline of the latter and of their nuclei is less sharp than normal, and they stain indifferently (dropsical degeneration, p. 25). Dropsical fluid differs somewhat in composition from different regions and under different conditions. It is usually a pale-yellow, clear, transparent, albuminous liquid, occasionally depositing fibrin or coagulating on standing (*e. g.* hydrocele fluid), rarely containing blood or an appreciable amount of structural elements, merely a few leucocytes and other cells. It differs considerably from the blood-serum and distinctly from normal lymph. The following table illustrates these variations:[1]

Fluid.	Parts per 1000.			
	Solids.	Water.	Proteids.	Salts.
Blood-plasma . .	97·10	902·90	82·89	8·55
Pleuritic fluid . .	36·05	963·95	28·50	7·55
Ascitic fluid . .	39·51	960·49	29·73	5·94
Hydrocele fluid .	61·15	938·85	50·05	9·26
Normal lymph . .	13·66	986·34	3·37	8·78

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[1] See Halliburton's *Text-Book of Chemical Physiology*, pp. 334–349.

FORMS OF DROPSY.

Five forms of dropsy may be recognised—

(1) Œdema of engorgement.—This is the result of disturbance of the circulation leading to venous engorgement or "passive congestion." If the venous outflow be obstructed, blood accumulates in the tissues and organs, fluid transudation from the capillaries is increased, and for a time may be compensated by increased absorption, but ultimately more fluid transudes than can be absorbed and dropsy ensues. This form of dropsy may be local or general, and is seen in obstruction to the great veins by (*a*) pressure from without, tumours and the like; (*b*) thrombosis (from inflammation, etc.), as in phlebitis, "white leg" after parturition, and the like; (*c*) engorgement and dilatation, with incompetence of the valves as in varicose veins; (*d*) in the portal vein from compression of its radicals by cirrhosis of the liver, and (*e*) in chronic cardiac disease ("back-pressure symptoms"). In the last named, so commonly seen in the later stages of mitral disease, the engorgement gradually passes backwards, first involving the left auricle, then the pulmonary circulation, and finally the right heart, but it is not until tricuspid incompetence occurs that the general venous system becomes the seat of engorgement. Gravity also aids, and hence this form of dropsy is first noticed in the most dependent parts, the ankles.

(2) Inflammatory œdema accompanies inflammation in a part, and is circumscribed and local. The exudation is richer in proteid than the other forms, contains more cells, and has a greater tendency to coagulate.

(3) Hydræmic or cachectic dropsy occurs in renal disease, in anæmia, and in cachectic states, with or

without anæmia, such as diabetes, advanced tuberculosis, and malignant disease. The true renal dropsy is seen in any loose tissue, and is independent of gravity, being often first observable about the face, and particularly in the eyelids. The extensive dropsy occurring in the later stages of renal disease is largely due to cardiac failure.

(4) ANGEIONEUROTIC ŒDEMA.—In certain cases of spinal disease, in exophthalmic goitre and erythromelalgia, in urticaria and erythema nodosum, more or less localised œdema occurs. It often comes on with surprising rapidity.

(5) LYMPHATIC DROPSY.—Obstruction to the outflow through the lymphatics is not a frequent cause of dropsy. The lymphatic anastomosis is very free, and even if the thoracic duct be occluded collateral channels may be opened up and prove sufficient. Moreover, the blood-vessels themselves have the power of re-absorbing the transuded fluid if the excess be not too great. If the thoracic duct be occluded and no compensatory channels be opened up, ascites results, and if a communication between the duct and the peritoneal cavity be established through rupture, the ascitic fluid becomes milky from admixture with chyle and the presence of fat (chylous ascites). This may occur in consequence of wounds, the pressure of tumours, etc. In some instances the pleural cavity may be the seat of the effusion. Obstruction to the lymph-channels by the embryos of the filaria gives rise to much œdema, as in lymph scrotum and the various forms of elephantiasis. In some instances from the same cause a communication is established between the abdominal lymphatics and the urinary tract and *chyluria* is the result, the urine becoming similarly milky and containing fat. Occasionally the wounding of a large lymphatic trunk may lead to the establish-

ment of a fistula discharging lymph, *lymphorrhagia*. Œdema is present to a slight extent in myxœdema, but is here due to an increase in the amount, or perhaps to some mucinoid change or degeneration, of the connective tissues.

PATHOLOGY OF DROPSY.

The normal production of lymph is generally held to be due to a combined process of filtration, dialysis, and osmosis through the capillary vessel-walls, and to be dependent on the difference of pressure between the blood in the vessels and the fluid in the extra-vascular tissue spaces, the production of lymph rising and falling as the capillary pressure increases or diminishes. It is found that the same variation in pressure causes a different amount of transudation in different situations. Thus, in the limbs the capillaries offer a considerable resistance to the transudation of fluid, those of the intestines are more permeable, and those of the liver still more so. Hence it is assumed that the permeability of the vessel-walls, their resistance to the passage of fluid, varies in different regions, and is another factor that has to be taken into account. The notion that the endothelium possesses a secretory function is not now generally held by physiologists.

Filtration in the living organism is a process different from that which usually obtains in the laboratory, the filtering medium being a living membrane with fluid on both sides of it. Under these conditions the amount of crystalloids filtering through varies *directly* with the pressure, but that of colloids, like proteid, *inversely* with the pressure. *Dialysis* is the passage of crystalloids through a permeable membrane, *e. g.* parchment, which separates them from water or a solution containing less crystalloid. Simultaneously with the passage of crystalloids *out,* water passes *in* ; this is *osmosis,* and if the process be conducted in a bladder connected with a manometer, the pressure in the bladder is found to rise considerably ; this is the *osmotic pressure.* Osmosis is theoretically possible without dialysis (though the latter, to a small extent, always does occur, all artificial membranes being to some degree imperfect), but dialysis is always accompanied by osmosis.

Theories of Œdema Formation.

An old view of the occurrence of dropsy, particularly in renal disease, was that it is due to a watery condition of the blood, hence the term "hydræmic dropsy." But it may readily be shown that a watery condition of the blood (hypalbuminosis) alone is not sufficient to cause dropsy, for the injection of large quantities of physiological salt solution into an animal is followed by no trace of œdema.

Cohnheim taught that the production of œdema essentially depends on one or both of two factors—(1) rise in blood-pressure, and (2) increased permeability of the vessel-walls. As regards passive œdema, he considered that increased blood-pressure alone sufficed, but he believed that the other forms of œdema depended upon increased permeability of the vessel-walls. Heidenhain found that the intra-vascular injection of certain substances, such as enzymes, egg-albumin, and extracts of crab-muscle, produced marked transudation from the vessels, and concluded that stimulation of the secretory function of the vascular endothelium formed the basis of œdema formation. As already stated, a secretory function of the vascular endothelium is not now admitted by most physiologists. Hamburger modified

Heidenhain's theory by suggesting that endothelial hypersecretion is due to waste products in the blood which accumulate as the result of venous obstruction.

Lazarus-Barlow concludes that in all cases in which œdema occurs there is a starvation of the tissues and an accumulation in them of waste or metabolic products, and that œdema formation is an excess of the normal processes whereby the nutrition of the tissues and the removal of their waste products are carried out, and inclines to the view that a vital secretory activity of the endothelium is a necessary factor in the process.

Increased arterial pressure alone does not give rise to œdema as long as the venous return is unhindered, but in passive congestion there is an increased transudation, which frequently results in dropsy. Œdema of venous congestion is also often seen as a result of the interference of venous outflow from a part by thrombosis of, or the pressure of a tumour on, a large vein, the causal relationship between the two phenomena being seen by the disappearance of the œdema on the removal of the obstruction. Yet, the ligature of a large vein, such as the femoral in the dog or in man, never causes a trace of œdema.[1] Both in increased arterial pressure and in venous obstruction produced by a ligature there can be no doubt that the capillary blood-pressure is raised and increased transudation occurs, but is carried off by the lymphatics. If, however, previous to the ligature of the femoral vein in a dog, the animal be brought into an abnormal condition by repeated bleedings, the injection of a large amount of saline solution, or the injection of poisons such as arsenic, or, locally, by a preliminary ligature of the femoral artery, or the production of inflammation in the paw by immersion in hot water, then œdema follows on ligature of the vein.

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[1] See Starling, *Path. Soc. Trans.*, vol. lii, 1901, p. 123.

That is to say, increased capillary pressure does produce œdema provided there is at the same time some factor modifying the vitality of the vascular endothelium. If the last-named be present, œdema then occurs if there be even a slight rise in capillary pressure, and this theory has been advanced to explain the pathology of most varieties of œdema. As regards chronic heart-disease, with failure of compensation, there is stagnation of blood and consequent impairment of the vitality of the vascular endothelium, though that under such circumstances there is an *increase* in the capillary pressure must be doubted. As Starling points out, in simple heart failure there is, to begin with, a fall of capillary pressure in the extremities (where this normally amounts to about 20 mgr. of mercury), but any failure of the blood-supply excites the vaso-constrictor centres and causes general vascular constriction throughout the body, with a rise in capillary pressure in the liver.

As regards the œdema of passive congestion, as in heart-disease, Starling considers that a rise in capillary pressure cannot be made responsible for the œdema—at any rate, in the extremities—the main factor being, not increased pressure, but diminished circulation and, therefore, damaged capillary endothelium. The stagnation of the blood, particularly in the most dependent parts of the body, so alters and augments the permeability of the capillaries that any slight increase of pressure within them, such as that due to mere change of position, is sufficient to cause a transudation greater than can be carried off by the lymphatics, and œdema of dependent parts is the result.

Experiments on the production of hydrothorax confirmed the results arrived at with regard to œdema of the connective tissues. No amount of increased capillary pressure produced a trace of fluid in the pleura unless the pleural membrane were first damaged, as by the injection of jequirity proteids, when extensive and often fatal hydrothorax rapidly ensued; similar results were obtained with the peritoneum. Obstruction of the thoracic duct and production of hydræmic plethora by saline injection induced a moderate amount of ascites, but very little effect followed obstruction of the inferior vena cava or partial obstruction of the portal vein. Under such circumstances, however, slight damage to the peritoneum, *e. g.* by immersing some coils of intestine in tap-water for a few minutes, causes in a few hours a copious effusion.

Starling therefore regards an alteration in the capillary walls leading to increased permeability, aided or not by increased capillary pressure, as the basis of œdema formation. As already stated, the capillaries in different regions show great variation in permeability, those of the liver being most so, and this fact perhaps explains the frequency and extent of ascites in many cases of dropsy.

Another observation suggests an alternative mechanism in the production of hydrothorax in certain instances. Filling the carotid sheath with saline solution and allowing it to trickle thence into the superior and posterior mediastina, under the influence of the respiratory movements the fluid was sucked into the pleural cavities through an apparently intact endothelium.

With regard to renal dropsy, very probably the same poison which, circulating in the blood, causes the renal inflammation, causes also damage to the vascular endothelium, with increased permeability. It may also be aided by a rise in capillary pressure, but this can hardly be operative in the early stages. We cannot explain the distribution of the œdema (*e. g.* of the face, which is so often first affected) otherwise than by assuming that in certain regions the capillary endothelium is more vulnerable. It is interesting that in urticaria the same distribution is often seen, the face frequently being involved first. In the later stages of renal dropsy the œdema is generally largely owing to cardiac failure, *i. e.* it is due to passive congestion.

Another condition in which œdema similar to the renal is seen is beri-beri. It can hardly be doubted that in this disease there is a poison circulating in the blood, which is partly responsible for the dropsy, though passive congestion from cardiac failure and dilatation also plays a considerable part.

Angeio-neurotic œdema we know little about. Any direct influence of the nervous system on the vascular endothelium is not generally admitted. It is true that section of a nerve supplying a part may determine the occurrence of œdema if other factors be present, but the influence is probably vaso-motor and not secretory. A poison circulating in the blood is a likely explanation, and seems to be the case in urticaria. Wright has also found that the blood is frequently deficient in coagulative power in these cases.

In inflammatory œdema endothelial damage is obvious, considering the blood-stasis that occurs and the presence of the exciting cause, *e. g.* bacterial products.

To sum up, in all the forms of œdema or dropsy damage to the capillary endothelium may be present, and this damage may be regarded as inducing increased permeability. A rise in capillary pressure will, under these circumstances, increase the transudation, but is not necessary and is often absent. Starling considers that with the increased permeability the ordinary factors of osmosis and filtration are sufficient to cause the abnormal transudation. Some would ascribe a secretory function to the vascular endothelium, but most physiologists do not admit this.

CHAPTER VIII.

SHOCK AND COLLAPSE.

Shock and collapse are conditions which, in their clinical symptoms, closely resemble each other, but which, in their pathology, are quite different. In both the subject is profoundly prostrated, he lies quietly in a somnolent condition, but he is not insensible—at least, until the last; for he can be roused for a brief period, and will answer questions correctly, though often not above a whisper. His face is pale and shrunken, his eyes hollow, and nose, lips, and ears blue. The skin is cold, often moist, with a cold, clammy sweat, but the lips and tongue are dry, and thirst is complained of. The respiration is shallow, irregular, and sighing, the heart's action feeble and rapid, the pulse fluttering or imperceptible, and the temperature sub-normal. The secretion of urine is diminished or suppressed, but the muscular power is largely retained.

The causes of shock and of collapse are different. Shock is an affection secondary to some severe injury, particularly abdominal, *e.g.* the crush of a limb, contusion of the abdomen, rupture of a viscus or aneurysm, perforation, volvulus, or acute strangulation of the bowel. Susceptibility to shock varies with different races and individuals. The Egyptians and Sudanese are relatively insusceptible, and therefore bear operations remarkably well, while neurotic and highly sensitive individuals suffer greatly. Pain is a factor in the production of shock, but shock may occur without pain. Injuries of the brain are potent in producing shock, and the first stage of concussion is simply a state of extreme shock.

Collapse generally ensues in the course of some acute or chronic disease, *e. g.* cholera, profuse diarrhœa, severe vomiting, and it may also succeed shock.

Shock is due to centripetal impulses from the seat of injury which cause inhibition of the tonic action of the vasomotor centres with enormous dilatation of the smaller vessels, especially in the splanchnic area, and fall in blood-pressure. The blood cannot really fill the whole of the vessels if these be dilated, and the individual, therefore, practically bleeds into his abdominal vessels. The result of this is, that the heart does not receive the proper quantity of blood, its action becomes feeble, and anæmia of the brain results, which further reacts on the body generally. The centripetal impulses also probably act directly on the cardio-inhibitory centres, and cause feebleness or arrest of the heart's action.

Loss of fluid, *e. g.* by vomiting or diarrhœa, nearly always precedes collapse, and collapse is regarded as due to a loss of fluid by the tissues of the body. It can be shown that in collapse there is a steady rise in the specific gravity of the tissues and blood, showing that there is abstraction of water, and in cholera the blood may be actually viscid from this cause.

CHAPTER IX.

DISORDERS OF METABOLISM — METABOLISM — ATROPHY — OBESITY — URIC ACID DYSCRASIA — GLYCOSURIA AND DIABETES MELLITUS.

CERTAIN disorders, the main features of which are abnormalities of metabolism, and which cannot be referred to any particular pathological state or condition, may, for convenience, be termed disorders of metabolism. The principal of these are general atrophy, obesity, gout, and diabetes. Other diseases, such as renal disease and leukæmia, are associated with changes in metabolism, but since pronounced pathological lesions of various organs or tissues are to be found in these, they are considered elsewhere.

GENERAL ATROPHY.—In order that an animal may be properly nourished and not lose weight, it is necessary that it be provided with not less than a certain minimum of proteids, carbohydrates, fat, salts, and water. The proportion of these constituents may to some extent be varied so that one may in some degree replace the other; this is true as regards proteids, carbohydrates, and fats. A certain minimum of proteid is necessary to maintain nitrogenous equilibrium, and make up for nitrogenous waste and excretion; if this be withheld, the animal feeds on its own proteids, loses weight, and starvation ensues. On the other hand, a diet consisting solely of proteid, though it contains all the constituents necessary for perfect nutrition, is wasteful, as two or three times the amount necessary to supply the nitrogenous requirements are requisite, and in man, at any rate, such a diet soon leads to digestive disturbance and has to be discontinued. In dogs the saving effect of fats and carbohydrates on the amount of proteid necessary can readily be shown; if fats be given, the animal requires some 7 per cent., and if carbohydrates, some 10 per cent., less proteid. Glucose is, therefore, a valuable food and of considerable value in neutralising tissue waste in fever patients. Adult animals supplied with water alone live for from four to five weeks; there is a gradual loss of weight down to about one half, the excretion of carbon dioxide and of urea falls, the former continually until death ensues, the latter considerably for from four to five days, and then remains at a constant low level until the end of the fourth week, when, shortly before death, there may be a sudden rise, and practically the whole of the fat disappears.

The following has been stated to be a perfect diet, the individual neither gaining nor losing weight:

			Grams of Nitrogen.	Grams of Carbon.
Proteids	100 grams	=	15·5	53·0
Fats	100 „	=	—	79·0
Carbohydrates . .	240 „	=	—	90·0
Salts and water .				
			15·5	222·0

Gelatin, though rich in nitrogen, cannot be used as a complete substitute for proteid, but the amount of proteid required is lessened if gelatin be given at the same time; it is a proteid sparer.

It has long been accepted, especially from the work of Ranke and Voit, that a man requires a minimum of 15–18 grams of nitrogen in his daily food, as stated in the foregoing table. But some recent work by Chittenden and his pupils suggests that something like half this amount of nitrogen is sufficient to preserve physiological equilibrium. If Chittenden's results be confirmed, in the sense that man can get on just as well with this reduced intake of nitrogen, we shall have to revise our diet tables, and the change will make both for economy and health.

Another fact of importance in considering metabolism is, that recent work seems to show that the proteid molecule is much more completely broken down by the digestive process than used to be supposed, particularly by the intestinal enzyme erepsin, which decomposes peptone into amino-acids, etc., and it appears likely, therefore, that proteid and protoplasm are built up or synthesised in the body from comparatively simple products.[1] It has been shown that animals may maintain their health, weight, and normal nitrogenous metabolism by feeding them on the crystalline cleavage products resulting from pancreatic digestion. The synthesis of the simple products seems to take place in the intestinal epithelium.

Although this appears to be the manner in which the body habitually forms its proteid, if the simple substances are not present it still seems able to make use of intact proteid molecules, possibly by means of enzymes which are present in all tissues.

General atrophy may ensue from starvation, due either to withholding of food or because the food cannot be absorbed or retained. In cases of stricture of the œsophagus no food can reach the stomach and the individual necessarily must be starved unless relieved. Similarly in persistent vomiting or diarrhœa, from disease of the stomach or bowel, in pregnancy, etc., the quantity of food digested and absorbed is insufficient to maintain nutrition and wasting and atrophy ensue.

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[1] See Halliburton, *Path. Soc. Trans.*, vol. lvi, 1905, p. 158.

In fever, atrophy occurs from two causes; there is increased tissue waste and there is diminished absorption of food owing to catarrh and general disturbance of the digestive tract. In some diseases unaccompanied with fever, cachexia may ensue owing to the presence of toxins, which similarly interfere with absorption and nutrition, *e.g.* the afebrile stages of syphilis. In malignant disease cachexia and atrophy are frequently present. When the disease is extensive this is easily explicable by the general disturbance of function caused thereby, but a comparatively small growth may cause pronounced cachexia and atrophy. This has not completely been explained, but it may be due to the production of toxins or to mal-digestion, the result of achlorhydria, which is present in carcinoma even when situated in parts distant from the digestive tract (Moore).

When there is an excessive discharge of proteid, as in renal disease, or of sugar as in diabetes, atrophy is often present, which is caused by general disturbance of function or the presence of toxins rather than by the actual loss of nutritious stuff.

There are, however, cases of general atrophy in which no cause can be assigned except that metabolism itself is at fault, of which, however, the only proof that exists is the atrophy. Such are some of the cases of "living skeletons" which are exhibited.

Obesity.—In a sense the antithesis of general atrophy, general lipomatosis or obesity, may next be considered. The subject of fatty infiltration and degeneration of cells and tissue has already been discussed (see p. 31).

General obesity may be due to excessive amount of food, *i. e.* over-eating, the excess of absorbed food being largely stored in the tissues in the form of fat. Diminished oxidation is also a contributing factor—*e. g.* from diminished exercise, also in chronic heart and pulmonary diseases and anæmia. The most marked cases of obesity are generally due to a combination of factors, viz. over-eating, want of exercise, and excessive consumption of alcohol.

Cases are, however, frequently met with in which obesity is not due to over-eating. The condition not infrequently runs in families, and is sometimes associated with glycosuria. One disease, adiposis dolorosa, in which large deposits of fat occur, seems to be of nervous origin (p. 33). More or less obesity is common after middle life, particularly in women after the menopause; and castration of the male or spaying of the female in childhood is followed by deposition of fat; hence these operations are performed on animals intended for food. In some instances the thyroid is atrophic, and administration of thyroid extract reduces the obesity. These facts suggest that certain internal secretions may influence and modify metabolism. In those cases of obesity not due to any apparent cause, it can only be said that metabolism is at fault, possibly on account of the deficiency of an internal secretion, the quantity of fat formed from proteid being greater than normal. In the obese, oxidation is diminished, the intake of oxygen and the output of carbonic acid both being decreased.

Uric Acid Dyscrasia.—A disorder or group of disorders is associated with the excessive formation of uric acid. One of the chief of these is *gout* or podagra; migraine and neuralgias also often seem to be dependent on the same cause, while Haig and others, it can hardly be doubted, have exaggerated the importance of uric acid, and have ascribed all sorts of disorders to its presence in the body, a condition which has been termed *uricacidæmia*, or the *uric acid diathesis*.

Uric acid is probably formed in the liver (see p. 390), and is derived from "purin bases" of nucleo-proteids and nucleins of the food or of the body itself. Purins derived from the food are termed "exogenous," those from the tissues of the body "endogenous."

The derivation of uric acid from nuclein may be represented as follows:

Nuclein or Nucleo-proteid
- Proteid
- Nucleinic acid
  - Phosphoric acid
  - Mother substance or Purin
    - Alloxuric, xanthin, or purin bases.
    - Uric acid.

From the base purin ($C_5H_4N_4$), adenin ($C_5H_4N_4NH$), guanin ($C_5H_4N_4ONH$), hypoxanthin (mono-oxy-purin, $C_5H_4N_4O$), xanthin (di-oxy-purin, $C_5H_4N_4O_2$), and uric acid (tri-oxy-purin, $C_5H_4N_4O_3$) are derived. The relative amount of uric acid or of xanthin bases produced depends upon the degree of oxidation taking place; the greater the degree of oxidation, the greater the quantity of uric acid produced.

As regards food, the amount of purins is very variable, as shown by the following table:[1]

	Undried purins. Grams. per kilo.
Fish:	
Cod	0·582
Salmon	1·165
Meats:	
Tripe	0·572
Mutton	0·965

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[1] See Walker Hall, *The Purin Bodies*. (Lewis, 1902.)

	Undried purins. Grams. per kilo.
Veal	1·162
Pork	1·121
Beef	1·137–2·066
Liver	2·752
Sweetbread (thymus)	10·063
Chicken	1·295
Vegetables:	
Bread (white)	none
Beans (haricot)	0·637
Potatoes	0·020
Beverages:	
Pale ale	0·145
Wines (claret, port, etc.)	none
Tea	0·750–1·120
Coffee	1·700

From this it will be seen that white fish contains about half the purin that meat does; red and white meats, including chicken, do not differ notably in their purin content, though that of beef may be high (variations occur according as there is much or little fat); beans contain a good deal, but green vegetables little; eggs contain none; milk, butter, and cheese traces only; beer does not contain much, wine none, tea, and especially coffee, a good deal.

Since nucleo-proteid and nuclein are particularly abundant in the nuclei of cells, tissues rich in cells, such as liver and sweetbread, have the highest content of purin. In health the amount of uric acid excreted *per diem* varies from 0·2 to 1·4 grams, averaging 0·8 gram, the amount being dependent on the food.

Gout is a pathological condition associated with, if not dependent on, a retention of uric acid in the body. It is characterised by acute exacerbations, in which acute arthritis with fever occurs, and immediately before the attack the amount of uric acid in the blood is found to be excessive. The amount of uric acid excreted during the quiescent intervals is generally low, 0·4 gram or less *per diem*, but this is not necessarily the case; exceptionally it may be normal, or even excessive, but in these events excretion does not keep pace with production, and hence there is increased retention in the body..

An attack of gout is frequently preceded by premonitory symptoms, headache and depression, dyspepsia, palpitation, neuralgia, etc., and then a joint or joints become attacked with an acute arthritis, attended with moderate fever and acute pain, redness, and swelling of the affected joint. In the earlier attacks the metatarso-phalangeal joint of the great toe is generally the one affected, but afterwards the ankle, knee, wrist, finger joints, and elbow may be involved—the shoulder and hip rarely. The arthritis is due to the precipitation in the joint structures, mainly the articular cartilages, of crystalline sodium biurate, with traces of potassium, calcium, magnesium, and ammonium urates, and of calcium and magnesium carbonates and phosphates, and occasionally of hippuric acid. The sodium biurate chiefly occurs in the form of fine acicular crystals, less so as amorphous granules, and is deposited from the synovia. In all probability, owing to interference with the circulation, there is, to begin with, a patchy superficial necrosis of the cartilage, in which the sodium urate is deposited, the salt being much more abundant at the surface than in the deeper portion of the cartilage. The urates also become deposited in the ligaments and synovial membrane and other fibrous structures of the joint. The deposition of the salts is followed by hyperæmia and inflammatory exudation into the joint, which rarely becomes purulent, and then only as the result of infection. Between the attacks some of the salts may be removed, but recurrent attacks lead to a chronic condition, and the articular cartilages may appear as if smeared with whitening; a deposit of the urate is also frequent in the cartilage of the ear (tophi), in fibrous tissues about the smaller joints, particularly of the fingers (chalk stones), and in fibrous tissues generally—the sclerotic, meninges, etc. These deposits are liable to undergo necrosis and ulceration, with the discharge of the urate as a soft, chalky material. In the kidney, the urate may form scattered masses in the cortex, or streaks running parallel to the vasa recta; a good deal of sclerosis is generally present (the gouty kidney). A number of pathological conditions may complicate gout—calculi, renal and vesical catarrh, urethritis simulating gonorrhœa, arteriosclerosis, atheroma and phlebitis, asthma and other respiratory troubles, eczema, psoriasis, and pruritus, etc.; glycosuria also is not infrequent.

Several theories have been propounded to account for the deposition of the sodium biurate. Garrod first showed the presence of an excess of uric acid during a gouty attack by taking the fluid from a blister, or transudation fluid, acidulating with acetic acid and placing in the acid fluid some woolly threads, on which the characteristic uric acid crystals became deposited in twenty-four hours. Ebstein assumes that the necrotic areas in the joint cartilages are due to the presence of neutral urates, which act as toxins, and acids then being produced in the necrotic areas cause the formation of the biurate from the neutral urate, and he believes that the gouty paroxysm is due to diminished excretion of uric acid, but since this may go on for months without result, it can hardly be the cause of the acute attack. Pfeiffer has suggested that normally the uric acid produced in the blood and tissues is capable of destruction by the viscera, and that in gout this capacity is lost and a deposition of uric acid salts is the result. As long as the deposit of uric acid is in the form of sodium biurate it is unirritating, but if an increase in the alkalinity of the blood occurs, the stored up uric acid is brought into solution and gives rise to the irritation and pain.

The late Sir William Roberts studied very carefully the salts which uric acid forms and their solubilities, and his views are those which are most generally accepted in this country. According to Roberts, uric acid (U) can form with a monovalent alkali (M) three classes of salts — normal or neutral urates (M_2U), biurates (MHU), and quadriurates (H_2UMHU). The normal urates are formed only by the interaction of uric acid with *caustic* alkalies, and hence do not enter into consideration, since caustic alkalies are not present in the body. Normally, in the blood and urine, the uric acid is present in the form of a quadriurate, which is relatively soluble (1 part in 500 parts of serum) compared with the biurate (1 in 10,000 of serum). Sodium biurate, however, is more soluble in water at 37° C. (1 in 1000), the difference in dissolving power between serum and water apparently being due to the presence of sodium salts in the former. Sodium biurate also exists in two forms—one stable, anhydrous, and crystalline, the other unstable, hydrated, and amorphous, the latter being more soluble in serum than, and readily changing into, the crystalline. The quadriurate, on standing, slowly changes into the crystalline biurate, passing through an intermediate stage of the amorphous biurate, and the rate and readiness of the change from quadriurate to crystalline biurate depend, partly on the quantity of quadriurate, and partly on the quantity of sodium salts present. The greater the quantity of quadriurate present the more rapidly does the change take place, and this is also hastened by the addition of sodium salts. Sir William Roberts concluded, therefore, that an attack of gout occurs when the synovia and lymph are being highly charged with uric acid (*i. e.* quadriurate); under these circumstances, there is an increased proneness to the formation of the biurate, which is aided by an excess of sodium salts.

These theories, although they explain more or less perfectly the cause of the gouty attack, do not explain the cause of the increased formation of uric acid and its retention within the body. In some cases, particularly when there is renal disease, the excess in the body might be referred to diminished excretion, but far more frequently there is excessive production. It has been suggested that the excess is the result of a disordered process of nitrogenous metabolism, which becomes arrested, and instead of urea ultimately being formed, uric acid is the product. But in most cases there is no evidence that the excretion of urea is deficient. Excessive consumption of nitrogenous food and deficient exercise are often met with in gouty persons, and the increase in uric acid might thus be accounted for, but it would seem that the consumption of alcohol is of still greater importance, and in the gouty a moderate amount of a fruity wine or of beer will often precipitate an attack. Moreover, gout in many instances is markedly hereditary, and is frequently associated with glycosuria; and all these facts suggest that the disease is due to a fault in metabolism, perhaps in the metabolism of the liver, and that in most instances an increased formation of endogenous purins, and not an increased intake of exogenous purins, lies at the root of the disease. That is to say, there appears to be an increased disintegration of the body nucleo-proteids in gout, and the gouty attack may be considered to be due to an increase in the quadriurates circulating in the blood, these being derived from some sudden disintegration of cells of the body that are rich in nuclein.[1] That the uric acid is derived from the disintegration of nucleo-proteid is further confirmed by the rise in excretion of phosphoric acid during the attack; the nucleins being rich in phosphorus, their disintegration and oxidation are accompanied by an increase in the excretion of phos-

Case I.

Date.	Urine in c.c.	Sp. Gr.	Uric acid.	Phosphoric acid.	Remarks.
Feb. 1-2	870	1009	0·0269	0·5410	Feeling well; no acute symptoms.
„ 2-3	1560	1008	0·1489	—	
„ 3-4	2110	1008	0·1297	—	
„ 4-5	2320	1005	0·0893	0·7420	
„ 5-6	1630	1004	0·0210	0·2450	Acute arthritis right knee began to-day. Fever lasting 8 days; highest temp. 101° F.
„ 6-7	1490	1010	0·0266	0·2730	
„ 7-8	1390	1008	—	0·8790	
„ 8-9	1780	1011	0·3867	1·8230	
„ 9-10	1660	1012	0·3984	1·4200	
„ 10-11	1860	1013	0·5487	2·1920	Acute symptoms persist.
„ 11-12	1720	1013	0·3887	1·7730	
„ 12-13	2260	1011	0·3921	—	
„ 13-14	1620	1010	0·4829	1·5860	
„ 14-15	2330	1007	0·4729	1·4780	Symptoms subsiding.
„ 15-16	1720	1009	0·3921	1·3990	
„ 16-17	1320	1007	0·2310	0·9870	
„ 18-19	1030	1013	0·0906	0·8230	
„ 19-20	540	1012	0·0729	0·5320	Patient feeling well; out of bed.
„ 20-21	440	1011	0·0774	0·4430	

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[1] Futcher, *Practitioner*, August, 1903, p. 181.

phoric acid, and just as the excretion of uric acid is generally below the normal in the intervals, so is the excretion of phosphoric acid below the normal. The accompanying abstracts of tables of analyses by Futcher

CASE III.

Date. April.	Urine.	Sp. gr.	Total nitrogen.	Uric acid.	Uric acid nitrogen.	Uric acid N to total N.	P_2O_5.	Remarks.
12-13	1330	1017	12·3390	0·3285	0·1095	1 : 112	0·5719	Patient well.
13-14	1865	1012	15·1438	0·5166	0·1722	1 : 87	0·8325	
14-15	2035	1013	14·8555	0·4985	0·1661	1 : 89	0·9645	
15-16	1550	1014	11·7180	0·4154	0·1384	1 : 84	1·1160	
16-17	1800	1013	13·0320	0·4176	0·1392	1 : 93	1·1700	
17-18	1585	1014	11·1591	0·3883	0·1294	1 : 77	0·9020	Acute attack began to-day.
18-19	2220	1013	14·1192	0·5283	0·1761	1 : 80	1·4740	
19-20	2220	1012	14·6076	0·5150	0·1701	1 : 85	1·3630	
20-21	2000	1013	13·9200	0·5632	0·1877	1 : 74	1·6808	
21-22	3000	1010	16·3800	0·7230	0·2401	1 : 67	1·7520	Height of attack; now began to subside.
22-23	2510	1010	14·4674	0·6902	0·2300	1 : 62	2·0833	
23-24	1840	1011	13·6528	0·7139	0·2379	1 : 57	2·8336	
24-25	1210	1014	12·8100	0·5124	0·1708	1 : 74	2·9890	
25-26	—	—	—	—	—	—	—	Urine lost.
26-27	1620	1011	16·4430	0·5362	0·1787	1 : 92	9·0412	
27-28	1020	1015	10·4448	0·4661	0·1553	1 : 67	1·7380	
28-29	2140	1009	16·1804	0·5007	0·1669	1 : 96	2·3326	
29-30	1600	1009	12·0960	0·2928	0·0976	1 : 123	1·9040	No acute symptoms.
30- 1	940	1013	8·7420	0·1673	0·0557	1 : 156	2·0774	

(*loc. cit.*) illustrate very well the excretion of uric and phosphoric acids, etc., in gouty persons :

The first table shows: (*a*) the exceptionally small excretion of uric acid in the well intervals, (*b*) the large excretion of uric acid during the acute stage, and (*c*) the manner in which the excretion of phosphoric acid follows that of the uric acid. This is still better seen if a curve be plotted on squared paper.

In Case III, in the well intervals the uric acid excretion was on an average a little below 0·4 gram *per diem*; during the acute attack the uric acid excretion became nearly doubled. There is a similar coincidence between uric acid and phosphoric acid excretions as in Case I, but the parallelism is not so exact.

There is some connexion between gout and chronic lead-poisoning, but the nature of the relation is not clear. Chronic lead-poisoning induces chronic renal disease, and may, therefore, partly act by diminishing excretion, or it may interfere with metabolism in the liver.

GLYCOSURIA AND DIABETES.—Normally the urine is practically free from carbohydrate; if this be present, the amount is too small to be detected by the ordinary tests. The carbohydrate most often found and of by far the most pathological importance is d-glucose,[1] but occasionally small quantities of other carbohydrates are met with, viz. lævulose, maltose, lactose, pentoses, and glycogen. Inosite also occurs, particularly in diabetes insipidus (p. 414), but although having the simple formula of a carbohydrate is really a benzine derivative (p. 409).

The usual tests for glucose are based on its reducing action upon copper and bismuth salts and picric acid, and the formation of a compound with phenylhydrazine having a characteristic crystalline structure and melting point. It must clearly be recognised, however, that reducing substances other than glucose are occasionally present in the urine, and in cases of doubt the fermentation test with yeast is the most simple and reliable. The reducing substance, not glucose, which is most commonly present is glycuronic acid (p. 408), and this is met with after the administration of many drugs and poisons, *e.g.* chloroform, turpentine, morphine and chloral, mineral acids, phosphorus, arsenic, and carbon monoxide. It is *not* fermented by yeast.

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[1] Dextro-rotatory glucose, also termed dextrose, glucose, and grape-sugar.

The presence of glucose in the urine is termed *glycosuria.* Glycosuria may be caused in many ways; it may be transitory or persist for a long period without other symptoms, particularly in gouty persons; this may be termed *glycosuria,* but frequently other symptoms are associated with glycosuria, viz. the passage of large quantities of urine up to 5 litres or more *per diem,* thirst, wasting, and a fatal issue, often with coma, within three years; this is *diabetes mellitus.* Pathologically, no distinction can be drawn between the excretion of glucose in glycosuria and diabetes, but clinically the two conditions are very different. The causes of glycosuria may first be discussed, after which diabetes may be considered.

Glycosuria may result from:

(1) *Excessive ingestion of sugar.*—Glucose, maltose, lævulose, lactose, and cane-sugar, if taken in large quantities, give rise to a transient glycosuria. Cane-sugar may also be excreted as such, but starch does not lead to glycosuria. Traces of lactose are not infrequent in the urine of suckling women (lactosuria). The appearance of glucose in the urine after ingestion of large quantities of sugar (100–200 grams) is termed *alimentary glycosuria* and is simply due to an excess which the normal metabolic processes have been unable to deal with.

(2) *Disease or extirpation of the pancreas.*—Total extirpation of the pancreas in dogs and cats leads both to glycosuria and to a condition resembling diabetes in man, viz. voracious appetite and thirst, wasting, polyuria, with the presence of acetone, diacetic acid, and β-oxybutyric acid in addition to the glucose, and a fatal issue within a few weeks—*pan-*

creatic diabetes. If a third of the pancreas be left these symptoms do not ensue, and if a fifth, glycosuria occurs only when carbohydrates are given in the food. That these results are not due to injury of the solar plexus or other sympathetic nerve-centres by the operation is proved by the fact that if a piece of pancreas be grafted into abdomen, and the pancreas be then removed the diabetic symptoms do not follow, nor do they if the pancreatic duct be ligatured or the secretion be conducted outside the body through a fistula. It has been surmised, therefore, that the pancreas has an internal secretion which presides over carbohydrate metabolism, possibly produced by the islets of Langerhans (see also p. 373). In a large proportion of cases of diabetes the pancreas is found to be diseased, and interstitial pancreatitis, cancer, and other diseases of the pancreas frequently occasion glycosuria.

(3) *Toxic states.*—It has already been mentioned that many toxic substances lead to the presence of glycuronic acid in the urine. A glucoside, phloridzin, derived from the root of the apple and cherry, when administered by the mouth or subcutaneously, gives rise to a glycosuria in which the amount of glucose excreted is out of all proportion to the amount of phloridzin administered, and the glucose is, therefore, not derived from the mere splitting up of the glucoside. Experiments by Pavy, Siau and Brodie[1] prove that the seat of formation of the glucose is the kidney, and that phloridzin probably acts by effecting a splitting up of proteid into a glucoside or carbohydrate moiety[2] which yields glucose.

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[1] *Journ. of Physiol.*, vol. xxix, 1903, p. 467.

[2] Pavy has shown that certain proteids contain a glucoside constituent.

(4) *Puncture of the floor of the fourth ventricle.*—It was shown years ago by Claude Bernard that puncture of the floor of the fourth ventricle in the neighbourhood of the vasomotor centre is followed by a transitory glycosuria. Other lesions of the nervous system lead to a similar result, *e. g.* tumours of the medulla and pons, injury of the vermiform process of the cerebellum, destruction of cervical sympathetic ganglia, division of the splanchnics, etc. In puncture glycosuria the glycogen in the liver is diminished, and the amount of sugar in the blood is doubled or trebled.

DIABETES MELLITUS.—Two classes of cases of diabetes may be recognised—one in which glucose appears in the urine only when carbohydrates are present in the food, the other in which glycosuria persists even when all carbohydrate is excluded from the diet; in the latter case, the glucose in the urine must be derived from proteid. The glucose excreted *per diem* may amount to 20, 50, 100, or even 200 grams, and the specific gravity of the urine is usually high (1025–1045) but not necessarily so. In addition to the sugar other substances are frequently present in the urine, viz. acetone, diacetic acid, and β-oxybutyric acid. The daily excretion of nitrogen is increased, it may be to double the normal or even more (30–40 grams). The respiratory quotient $\frac{CO_2 \text{ expired}}{O_2 \text{ inspired}}$ is diminished in the diabetic and is not appreciably increased by carbohydrate food, as is normally the case. Sugar is present in the blood in excess (*glycæmia*), it may be five or six times the normal, and when this is the case is excreted by the urine, a fact which can be demonstrated by injecting glucose into the jugular vein of an animal; in a short time the greater portion is excreted by the kidney.

It was comparatively recently that the relation of disease of the pancreas to diabetes was recognised, and up to that time two principal theories of the causation of the disease held the field. Bernard showed that the glycogen in the liver is readily converted into sugar, and he therefore supposed that the sugar derived from the food by digestion is intercepted in the liver and converted into glycogen, to be reconverted into sugar and passed on into the general circulation in accordance with the needs of the tissues, particularly of the muscles. Bernard concluded, therefore, that in diabetes an abnormal and excessive conversion of glycogen into sugar occurs in the liver, due to increased vascularity the result of vaso-motor disturbance. His discovery of "puncture glycosuria" supported this view. Pavy, on the other hand, regards glycogen as a stage in the conversion of carbohydrate into fat, and denies that the liver is a sugar-forming organ. According to his view, the sugar derived from the food by digestion should normally be converted into glycogen, and glycosuria results from a failure on the part of the liver to intercept the sugar, the sugar excreted in the urine being sugar derived from the food which has escaped conversion in the liver.

Cohnheim suggested that in diabetes there is a diminished destruction of sugar in the tissues, and held that the disease is due to "the absence of a ferment which, in a normal condition, initiates the further destruction of dextrose." This has been termed the *glycolytic ferment theory.*

A number of observations have shown that in a large proportion of cases (50–95 per cent. according to various authors) of diabetes disease of the pancreas is present. The lesion is usually of the nature of a fibrosis, and Opie and others hold that involvement of the islands of Langerhans is the essential cause of the glycosuria.

The islands of Langerhans are clusters of polygonal cells lying among the glandular acini of the pancreas, and it has been claimed that these islands are developmentally distinct from the pancreatic glandular tissue and have no relation to the ducts; very contradictory statements have, however, been made on this subject.[1] It has been supposed, therefore, that atrophy of the islands of Langerhans is the pathological basis of pancreatic diabetes, and it has been suggested that these structures normally secrete a glycolytic ferment, which, when absent (as in disease, or after excision, of the pancreas), permits the accumulation of glucose in the blood and its excretion by the kidney. Dale,[2] however, believes that the islands of Langerhans really represent stages in the functional activity of the secreting cells of the gland.

It is clear, therefore, from the foregoing that we are not in a position to formulate a single theory of the genesis of glycosuria and diabetes. In a large proportion of cases the fault lies in the pancreas, destruction of two thirds of which results in a glycosuria or mild diabetes, destruction of four fifths in a severe uncontrollable diabetic state. In others the disease may be of purely nervous origin; the results of experiment and the occurrence of glycosuria in certain cases of cerebral tumour support this. In others, again, the primary fault may lie in the liver.

Diabetic coma.[3]—Not infrequently diabetes mellitus terminates with coma. The onset is manifested by stupor, which increases and passes into coma, the temperature usually being subnormal, the respirations rapid and deep, and the heart's action rapid and feeble. The condition is obviously due to an intoxication, but with what has been the subject of much discussion. It has been ascribed to acetone [$(CH_3)_2CO$] and to di-acetic acid ($CH_3.CO.CH_2.COOH$), both of which substances are present in excessive amounts in diabetic urine, but it is practically certain that neither is the cause of the intoxication. Another and more likely theory is that the coma is the result of an acidæmia, or diminished alkalinity of the blood, and undoubted benefit is derived by the free administration of sodium bicarbonate by the mouth, or better, by intravenous inoculation. The acid content of diabetic urine is high, and is chiefly due to β-oxybutyric acid [$CH_3.CH(OH).CH_2.COOH$], of which as much as 20 grms. may be excreted *per diem*, but which, in itself, is not particularly toxic. The relation of acetone, di-acetic acid, and β-oxybutyric acid to one another is shown by the following structural formulæ:

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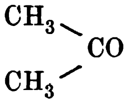
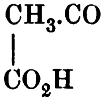
[1] See Reviews by Langdon Brown, *Practitioner*, August, 1905, p. 233, and Salisbury Trevor, *ibid.*, April, 1904, p. 570.

[2] See Bayliss and Starling, *Croonian Lect.*, Royal Society, 1904.

[3] See Douglas, *Brit. Med. Journ.*, 1903, vol. ii, p. 1629.

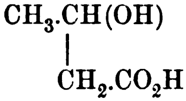


Acetone.



$$\begin{array}{l} CH_3.CO \\ | \\ CO_2H \end{array}$$

Di-acetic acid.



$$\begin{array}{r} CH_3.CH(OH) \\ | \quad\quad\quad \\ CH_2.CO_2H \end{array}$$

β-oxybutyric acid.

Usually also, the amount of ammonia in the urine is very high, the ammonia being required to neutralise the excess of the oxybutyric acid. The genesis of the coma is, therefore, explained as follows: The oxybutyric acid for its elimination requires a base, since it does not appear in the urine in the free state. It cannot, however, obtain sufficient soda and potash, and so makes use of the ammonia, which is derived from the metabolism of proteid, and which is normally destined to become urea. But if, as the result of gastric disturbance or of defective nutrition, this supply of ammonia be wanting, the acid utilises the alkali of the blood, acidæmia is the consequence, and stupor supervenes. It has been shown experimentally that the injection of large quantities of a dilute mineral acid induces coma and dyspnœa. It is, however, doubtful if this be the whole explanation.

Other substances have also been regarded as the cause of the coma, viz. β-amido-butyric acid, tri-methylamine, and paraldehyde.

CHAPTER X.

DISEASES OF THE DUCTLESS GLANDS AND ABNORMALITIES OF INTERNAL SECRETION.

THE THYMUS GLAND.[1]

The thymus gland is developed as a tubular diverticulum from the hypoblastic lining of the pharynx. Originally, therefore, epithelial in origin, it becomes invaded by connective and lymphoid tissues, and is transformed into a lymphoid organ, the corpuscles of Hassal being remnants of the epithelial structure.

It is composed of two lateral lobes, and the major part is within the thorax. From birth up to the age of two years its average weight is 7–10 grams, but at puberty it undergoes degeneration and atrophy, and in adult life is reduced to about 3 grams in weight. The function of this gland is unknown. Beard suggests that it is the parent source of all leucocytes, but this is unlikely, since Bryce has recently shown that in *lepidosiren* leucocytes are present before the thymus is developed. Henderson and Paton[2] have shown that there is a reciprocal action between the thymus and the testis, and probably also the ovaries (in cattle and guinea-pigs), each checking the growth of the other.

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[1] This section is largely taken from a Monograph by Dudgeon, *Path. Soc. Trans.*, vol. lv, 1904, p. 151.

[2] See *Journ. of Physiol*, vol. xxxii, 1904, p. 80.

Persistent hyperplastic thymus glands are not infrequent in exophthalmic goitre, and are occasionally met with in myxœdema, acromegaly, and Addison's disease.

Enlargement of the thymus is often present in the condition termed "lymphatism," in which sudden death occurs from trifling causes (see p. 244). This result has been ascribed to suffocation from pressure, intravascular clotting, or toxæmia due to thymic products, etc., but there is little to support either theory.

Enlarged thymus is also met with in a form of laryngismus or spasmodic dyspnœa (see p. 297), the thymic asthma, but the ordinary laryngismus so frequent in rickety children is probably not usually due to this cause (Osler).

Premature atrophy of the thymus is met with in wasting diseases of children and in "marasmus," fibrosis, endothelial, and small giant, cells being present. Tuberculosis of the thymus occasionally occurs. Congenital syphilis has been stated by Dubois to involve the thymus, but this is "not proven" (Coutts and Dudgeon). Carcinoma and sarcoma have been met with.

THE THYROID GLAND.

The thyroid gland consists of two lateral lobes united towards their lower ends by the isthmus. Each lobe extends from the side of the thyroid cartilage to the fifth or sixth tracheal ring, and measures about 5 cm. in length, 3 cm. in breadth, and 2 cm. in maximum thickness. The weight of the whole gland is 32-60 grams; it is generally larger in females, and frequently enlarges at the menstrual period. It is invested by a thin capsule of dense areolar tissue, which penetrates the substance of the gland, imperfectly dividing it into small lobules of irregular shape.

The thyroid consists of numbers of closed vesicles or acini, sphe-

roidal or polyhedral in shape, and varying in size from 0·03 to 0·05 mm. The alveoli are lined with a single layer of cubical cells, and the central portion is filled with the so-called colloid, which contains a nucleo-proteid and a globulin-like proteid containing iodine (thyroiodine). There are also, either imbedded in the thyroid as in man, or distinct from but adjacent to it as in the cat and dog, other glandular structures, which have received the name of the parathyroids. These consist of solid columns of epithelial cells, with strands of vascular connective tissue. Vincent and Jolly[1] believe that parathyroid tissue may develop into thyroid and that the parathyroids are embryonic thyroids. The thyroid is developed as a median invagination from the floor of the pharynx, the parathyroids as thickening of the epithelium on the dorsal aspect of the third and fourth visceral clefts.

The thyroid gland seems to be necessary for life. Its removal is followed by a train of symptoms followed by death, and atrophy or disease of the thyroid in man is attended by serious disorder or mal-development. This was proved, first by Kocher in 1883, who observed that complete removal of the thyroid for goitre was followed in 66 per cent. of the cases by all the symptoms of myxœdema, then by Horsley in 1885, who found that removal of the thyroid body in monkeys produced myxœdema, and finally by Murray in 1891, who showed the beneficial effect of thyroid extract in myxœdema. Since then a number of researches seem to show that extirpation of the parathyroids, the thyroid remaining intact, is followed by acute symptoms simulating tetany, while extirpation of the thyroid, leaving the parathyroids untouched, is followed by chronic symptoms, cachexia, myxœdema and cretinism. Horsley, in his experiments, also observed different effects in different animals on the removal of the thyroid; in monkeys myxœdema followed, while in cats and dogs acute symptoms, with tetany, developed. This difference may, perhaps, be attributable to the relation of thyroid and parathyroid in the last-named animals, and

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[1] *Journn. of Physiol.*, vol. xxxii, 1904, p. 65.

Horsley, though aware of the existence of the parathyroids, does not seem in his work to have differentiated between the two glands.

Although the views just stated as to the effects of removal of the thyroid are generally accepted, it must be confessed that there is some good experimental evidence which does not support them. Thus Vincent and Jolly (*loc. cit.*), as the result of one hundred experiments on cats, dogs, foxes, monkeys, rats, guinea-pigs, and rabbits, state that it cannot truly be said that either thyroids or parathyroids are essential for life, since it is frequently possible to remove either or both without causing death. In no animal did symptoms resembling myxœdema supervene, and Vincent and Jolly therefore conclude that myxœdema and cretinism must be due to causes more complex than mere thyroid insufficiency. Edmunds[1] has found that removal of the thyroid and parathyroid is followed by marked chromatolysis of the Nissl bodies in the motor ganglion cells in the cord. Neither thyroid nor parathyroid extract produces any distinct effect upon the blood-pressure.

MALFORMATIONS.—The thyroid gland is often irregular in lobulation. The isthmus may be absent, and accessory thyroids are not uncommon. The lumen of the pharyngeal diverticulum may persist as the thyrolingual duct, which may become dilated into a cystic cavity, and may open spontaneously in the median line of the neck. The gland is markedly hypoplastic or occasionally absent in cretins, and atrophy occurs in myxœdema and in old age. Regeneration and compensatory hypertrophy occur to a considerable degree after the removal of the greater portion of the gland.

Congestion of the gland may be present in chronic cardiac disease, compression of the veins in the neck, etc. Hyperæmia occurs in exophthalmic goitre, sometimes during menstruation. Inflammation is very infrequent and is generally secondary to traumatism. Tuberculosis, syphilis, actinomycosis, etc., occasionally occur.

GOITRE, bronchocele, or wen, is a term applied to any form of non-malignant enlargement of the thyroid. This is met with in certain districts in England, *e.g.* Derbyshire ("Derbyshire neck"), but particularly in some of the valleys of Switzerland and Italy. It may attain huge dimensions, and, from its size, obstruct respiration. It is more frequent in women than in men, and usually develops after puberty. The cause is not known with certainty, but water and telluric conditions are supposed to play a part. The usual form of goitre is due to a hyperplasia of the glandular tissue. In some cases there is no change other than the multiplication of the acini; in others the acini are larger and more irregular. Sometimes the acini are dilated and are filled with abundant colloid material (colloid goitre). The walls of the acini may be destroyed and large cystic spaces be formed. In other cases there is a marked dilatation of the blood-vessels and the gland may pulsate (vascular goitre, and in exophthalmic goitre). Occasionally the enlargement of the thyroid is due to an adenomatous proliferation of the glandular elements. Secondary changes may ensue in a goitre, fibrous tissue may become much increased (fibrous goitre), cysts may result from hæmorrhage and may finally contain a serous or brownish fluid containing cholesterin. Calcification is common in the walls of the cysts. Rarely proliferative changes may take place in the walls of the cysts, causing papillomatous projections.

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[1] *Path. Soc. Trans.*, vol. liii, 1902, p. 343.

Exophthalmic goitre, Graves' or Basedow's disease, which is much more frequent in women than in men, and is often associated with mental strain, is characterised by enlargement of the thyroid, tachycardia, and exophthalmos. The enlargement is largely due to vascular dilatation, but there is often in addition a round-celled infiltration, which may progress to fibroid induration, but otherwise there is little departure from the normal.

MacCallum[1] has recently given a detailed description of the changes met with in the thyroid in this disease, of which the following is an abstract:

The alveoli vary greatly in size and form, many of them showing remarkable folding of the epithelium, so that the cavities have the appearance of sending off long diverticula. Frequently, these diverticula become constricted from the remainder, and new alveoli are thus formed.

Changes in the epithelium consist, in general, in an alteration from the flat or cubical type to the high cylindrical form. The cells show frequent mitotic figures, and there are abundant granules of fat in their protoplasm. The cylindrical form is characteristic, but the height of the cells varies greatly. Occasionally, very large cells with very large vesicular nuclei occur in the walls of the alveoli, and are intercalated in the lining of cylindrical cells. The alterations in the colloid consist chiefly in its marked diminution in amount and in the ragged appearance of that which is present. The vascular supply is extraordinarily rich, the veins being especially large and distended with blood at the operation, although in the specimen as sent to the laboratory they are inconspicuous. The friability of their walls has been remarked upon by the operator. They lie imbedded, for the most part, in the very abundant connective-tissue framework of the thyroid, which is in all cases quite definitely increased in density, considerable bands of fibrous tissue being found to run through the gland and to cause a distinct lobulation of the tissue. In this interstitial connective tissue there is found also a great deal of lymphoid tissue in the form of circumscribed, scattered, lymphoid nodules, with definite *keimcentra* and well-defined architecture. The thyroids in many cases show the presence of circumscribed prominent nodules, sometimes in considerable number, which are composed of a more homogeneous tissue, and which on section are seen to be made up of uniform, small, round alveoli, usually widely separated from one another, and imbedded in a hyaline connective tissue. These are lined with plump, rather cubical, epithelium, and may or may not contain colloid material. These circumscribed nodules are found in other conditions of the thyroid, and are not characteristic of exophthalmic goitre. Cysts of various sizes, usually containing a clear greenish, somewhat glutinous, fluid may also occur.

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[1] *Johns Hopkins Hosp. Bull.*, vol. xvi, 1905, p. 287.

The parathyroid glands were examined in nine cases and were found to be practically normal in all.

On the whole the anatomical picture resembles most closely that produced by Dr. Halsted as a compensatory hypertrophy, and it seems probable that this may be explained by some previous injury to the gland, possibly from some foregoing infectious disease, such as influenza, etc., although a definite history of this kind cannot always be obtained. Similar changes may frequently be produced experimentally in dogs by the injection of some injurious material into the thyroid vessels, or even by the maintenance throughout a considerable time of a suppurative peritonitis in which, apparently by the diffusion of some poisonous substance, there occurs a destruction of many of the epithelial cells of the thyroid, which later are replaced by the compensatory hypertrophy of the remaining cells. The nature of the primary injury which may produce such a change in exophthalmic goitre is, however, by no means always clear.

The pathology of exophthalmic goitre is uncertain; by some it has been regarded as a neurosis or as a primary affection of the nervous system, by others the symptoms are considered to be due to an increased and perverted thyroid secretion, since total thyroidectomy may be followed by complete cure. The thymus is often enlarged in this disease.

Carcinoma of the thyroid occasionally occurs and is usually of a spheroidal- or columnar-celled type. Sarcoma has also been described.

Cretinism is a condition characterised by an arrest of mental and physical growth, and associated with hypoplasia or absence of the thyroid. It usually arises in the early years of life, but is occasionally congenital, and is met with in goitrous districts. If a rudimentary thyroid be present, it does not usually show the colloid material of the normal gland. The cretin is stunted, the lips thick, the skin dry and rough, the abdomen large and the genitals remain infantile, and the mental state is that of an imbecile. The condition occurs rarely in animals. Experimental removal of the whole of the thyroid tissue in a young animal is stated to be followed by a condition indistinguishable from cretinism, while the administration of thyroid gland or extract to a cretin is followed by an extraordinary improvement, showing that the disease is mainly due to absence of the thyroid secretion.

Myxœdema, a disease usually of middle age, and more frequent in women than in men in the proportion of 6 : 1, and characterised by a thickening, with dryness and roughness, of the skin and of the subcutaneous tissues, puffy, wax-like aspect of the face, somewhat simulating renal disease, and alteration of the features, the lips becoming thick, mental hebetude, heavy gait and subnormal temperature. It slowly progresses and ends fatally from some intercurrent affection. The disease was first observed by Gull and subsequently fully described by Ord.

This affection is always associated with changes in the thyroid gland, which is usually fibroid and atrophic, but other conditions which interfere with the production of the internal secretion may induce it. Since the administration of thyroid gland acts as a specific, the condition must largely depend on the absence of the internal secretion of the thyroid gland.

The name "myxœdema" was derived from the fact that in Ord's first case Charles found a large excess of mucin in the skin, fifty times more than normal, and it was therefore thought that a mucoid degeneration or transformation occurred in the disease. Subsequent research has not completely confirmed this. The amount of mucin in the normal tissues varies considerably, and is more abundant in the young. The following table gives the average of a number of analyses:

	Percentage of mucin.
Skin (children)	0·766
Skin (adults)	0·385
Connective tissues	0·521
Parotid Heart tendon	traces

Out of ten cases of myxœdema, Halliburton[1] found in two only an excess of mucin in the skin—viz. 0·81 and 6·72 per cent. respectively; in the remainder it was not more than normal, and the average of the ten cases was 0·374—*i. e.* approximately the same as in normal individuals. In monkeys, however, rendered myxœdematous experimentally by thyroidectomy, the amount of mucin is distinctly increased. Halliburton confirmed in a later paper[1] the fact that mucin is not necessarily in excess in myxœdema, and he points out that there is no doubt a connective-tissue overgrowth in the disease from which the mucin, when it is in excess, may be derived.

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[1] Report of a Committee of the Clinical Society, supplement to *Clin. Soc. Trans.*, vol. xxi, 1888.

A condition similar to myxœdema has been observed to follow complete extirpation of the thyroid gland in man, and in removal of goitres, etc., the surgeon is careful to leave a portion of the gland.

THE PITUITARY BODY OR HYPOPHYSIS CEREBRI.

The hypophysis is a small body composed of two lobes, an anterior and a posterior or infundibular. The anterior portion is composed of a glandular structure of tubules or alveoli lined by columnar epithelium, the posterior of large spindle-shaped and other irregular cells, some of which contain pigment. It occupies the sella turcica of the sphenoid bone and weighs 0·3-0·6 gram. The anterior lobe is developed as an up-growth from the stomodæum or primitive buccal cavity, the posterior as a down-growth from the floor of the primary interbrain in the region of the third ventricle, and the two portions, though closely connected, do not actually coalesce.

The pituitary body is almost constantly diseased in the condition known as acromegaly, and it has therefore been supposed to influence the growth of the body, particularly the bones.

Experimental removal of the pituitary is difficult, and the effects obtained are indecisive. The results of feeding young animals with pituitary extract and the use of this substance in acromegaly are also inconclusive. Schäfer and Oliver have found that extracts quicken the heart-beat and cause a rise of blood-pressure; it is very like the adrenal extract in this respect.

There may be some reciprocal action between the thyroid and pituitary, for the latter may enlarge after thyroidectomy and is often enlarged in diseases of the thyroid, in cretinism, and in myxœdema, but the extracts of the two glands have different physiological actions.

Pathological conditions of the pituitary are rare. Adenoma, carcinoma, and sarcoma have been described. Gummata and tubercles have also been recorded.

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[1] *Journ. of Pathol. and Bact.*, vol. i, 1893, p. 91.

Acromegaly.[1]—This is a disease first described by Marie in 1886 and is characterised by enlargement of many of the bones, coarseness of the skin, enlargement of the ears and tongue, and mental changes. The face is elongated on account of an increase in size of the superior and inferior maxillæ, particularly the latter, and the alveolar processes are widened and the teeth separated. The hands and feet are greatly enlarged, giving a spade-like appearance.

In almost all the cases the pituitary body is found to be abnormal. In some cases a tumour has been present, adenoma, sarcoma, or glioma, in others a simple hypertrophy, colloid degeneration, fibrosis, or vascular hyperplasia.

Marie considers acromegaly to be due to an abolition of the function of the pituitary; owing to this a toxic substance collects in the blood and leads to excessive osteogenetic activity. Tamburini regards the pituitary secretion as a growth stimulator, and an excessive amount of the secretion to be produced by the enlarging pituitary. Removal of the superior cervical ganglion in young animals produces overgrowth of the head and ear on the same side as the lesion. Cases of acromegaly have been described in which no lesion of the pituitary has been detected, also cases of enlargement of the pituitary without acromegaly, and it may, therefore, be that enlargement of the pituitary is only a contributing cause, possibly causing pressure on certain nerve-centres or tracts. Giants are usually acromegalic individuals (see p. 518).

The *pineal body* or gland is developmentally a remnant of a primitive dorsal eye. Hyperplasia, cysts, psammoma, and sarcoma have been described.[1] Melanotic sarcoma has been met with, an interesting fact in connection with its relation to an eye.

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[1] On Acromegaly, see Monographs in New Sydenham Society's series (*a*) by Marie; (*b*) by Sternberg; and papers by Furnivall, Neal and Smyth, Shattock, Rolleston, Dalton, and Hunter, in *Path. Soc. Trans.*, vol. xlix, 1898, p. 204 *et seq.*

THE ADRENALS OR SUPRARENALS.[2]

The adrenals are two flattened triangular bodies resting on the summits of the kidneys. They measure 3-4·5 cm. in length, 3 cm. in width at the base, and 0·5 cm. in thickness, and weigh 4-8 grams each, the usual combined weight being about 9 grams. Each adrenal consists of a cortical and a medullary portion. The yellow cortex is composed of large epithelioid cells, radially arranged in columns and becoming smaller towards the centre. The medulla is brownish, its cells are polygonal and oval, and stain brown with bichromate of potash, and it is permeated with large venous sinuses. The cortex seems to be mesoblastic and to develop from the Wolffian body, the medulla to be derived from the sympathetic ganglia and to become enclosed within the cortex.

A series of cases has been described in which in quite children a precocious development of hair and of the genitalia has been present and associated with hypertrophy or tumour of the adrenals.[3] Adrenalin on injection into mammals and birds produces glycosuria (not pancreatic).

Malformations.—Various abnormalities of shape and position occasionally occur. Accessory adrenals are not infrequent, and portions (adrenal rests) may become included in the kidney or liver. *Atrophy, fatty change, cloudy swelling,* and *focal necrosis* occasionally occur. *Lardaceous disease* is not uncommon in connexion with the same change elsewhere. *Hæmorrhage* into the adrenal may take place and is a marked feature in experimental diphtheritic poisoning (with toxin).

Tuberculosis is not infrequent, and *gummata* and *actinomycosis* have been met with. *Simple primary tumours* of the adrenals are usually adenomata, which are of two kinds—(1) multiple yellowish nodules in the cortex, not unlike tubercles, and (2) large single adenomata, also as a rule in the cortex. *Malignant growths* are generally large-celled sarcomata. The adrenal rests sometimes give rise to remarkable growths, especially in the kidney. Some of these are malignant and their structure more or less reproduces that of the cortex. Growths also occur in the pelvis, sometimes connected with the uterus, which also seem to be derived from adrenal rests.[1] Metastatic growths occasionally occur in the adrenals.

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[1] See Ogle and others, *Path. Soc. Trans.*, vol. l, 1899, p. 4 *et seq.*

[2] See Rolleston, "Goulstonian Lectures," *Brit. Med. Journ.*, 1895, vol. i, p. 629 *et seq.*

[3] See Bulloch and Sequeira, *Path. Soc. Trans.*, vol. lvi, 1905, p. 189 (bibliography).

ADDISON'S DISEASE, which is characterised by a peculiar bronzing of the skin (the pigment being in the cells of the rete Malpighii), asthenia, bradycardia, emaciation, vomiting, and diarrhœa, and progressing slowly to a fatal issue, is in the vast majority of cases associated with disease of the adrenals. Addison in 1854 first directed attention to this association.

The only common cause of the disease is a chronic fibro-caseous tuberculosis, but very exceptionally simple atrophy, chronic interstitial inflammation, malignant disease, or hæmorrhage may be the lesion present. Very rarely pressure or inflammation involving the semilunar ganglia has been present without lesion of the adrenals; generally both adrenals are affected, occasionally only one.

Extensive disease of the adrenals may be present, however, without the symptoms of Addison. A discussion of the pathogenesis of Addison's disease involves reference to the physiology of the adrenals.

The adrenals are necessary for life, and if both be removed the animals die, exceptions to this rule being due to incomplete removal or to the presence of accessory adrenals. Injection of extract of the adrenals produces a toxæmia. Oliver and Schäfer have shown that the medulla, and not the cortex, contains the physiologically active substance, the action of which is in large doses to cause acceleration and increase of the cardiac beat, shallow and rapid respiration, and lowering of temperature. Smaller doses cause slowing of the heart and enormous rise of blood-pressure, due to contraction of the arterioles. The contraction of voluntary muscle is greatly prolonged by the extract. Plain muscle may either contract or relax under the influence of adrenal extract, but only when sympathetic nerves are present.[1] Applied locally, the extract causes contraction of the vessels and blanching, and is, therefore, useful to control hæmorrhage. It stimulates glandular activity and may produce glycosuria, apparently by diminishing the utilisation of sugar in the tissues; the glycolytic power of the blood is lost. The active substance, adrenalin, can be extracted from the adrenals with water and is not destroyed on boiling. It is a crystalline body, probably a secondary alcohol, having the formula $C_6H_3(OH)_2.CH(OH).CH_2.NH.CH_3$.

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[1] See Eastwood, *Path. Soc. Trans.*, vol. liii, 1902, p. 153.

It seems highly probable, therefore, that the adrenals possess an internal secretion which presides over the general muscular tone. In Addison's disease we may presume that this secretion is in abeyance and hence the muscular weakness and prostration. It may well be also that the secretion, what remains, is perverted and perhaps causes the other symptoms, or that a toxæmia results in its absence.

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[1] Elliott, *Journ. of Physiol.*, vol. xxxii, 1905, p. 401. Brodie and Dixon (*ibid.*, vol. xxx, 1904, p. 476), found the pulmonary vessels to be unprovided with sympathetic vaso-constrictors and to be unconstricted by adrenalin. Hence adrenalin is not only useless in hæmoptysis but harmful, by raising the general blood-pressure, and therefore tending to increase the hæmorrhage.

CHAPTER XI.

DISEASES OF THE BLOOD, SPLEEN, AND LYMPHATIC GLANDS.

THE BLOOD.

The blood consists of a fluid plasma in which float corpuscles. The latter are of three kinds, the red or coloured corpuscles, chromocytes or erythrocytes, the white or colourless corpuscles or leucocytes, and the blood platelets. The blood is usually stated to amount to about $\frac{1}{13}$ of the body weight, but according to Haldane and Lorrain Smith[1] this figure is too high, and it should be $\frac{1}{20}$—$\frac{1}{22}$ of the body-weight.

Different terms are applied to variations in the constituents of the blood:

Increase in the number of chromocytes = polycythæmia.
„ „ „ „ leucocytes = leucocytosis.
Diminution in the number of chromocytes = oligocythæmia.
„ „ „ „ leucocytes = leucopenia.
„ „ amount of hæmoglobin = oligochromæmia.
„ „ total quantity of blood = oligæmia.

Anæmia (literally "bloodlessness") is a term used somewhat loosely, and includes oligæmia, oligochromæmia, and oligocythæmia.

In pathological conditions it is chiefly the corpuscular elements, and not the plasma, which vary, or perhaps it would be more correct to say that we know much more about the variations of the corpuscular elements than of those of the plasma in disease.

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[1] *Journn. of Physiol.*, vol. xxv, p. 331.

The specific gravity of the whole blood averages about 1059 for man and 1056 for woman. It does not vary much with drinking, it is diminished in anæmia, particularly in oligochromæmia, and in leukæmia, and is increased in conditions associated with diarrhœa, especially in cholera. The specific gravity of the plasma is much more variable, and is reduced in the anæmias and in chronic renal disease.

The rate of coagulation varies, and may be determined by Wright's coagulometer. It is reduced in the acute specific diseases, in the hæmorrhagic diathesis, and in pancreatic disease. The alkalinity of the blood also varies. It is reduced in gout, in acute rheumatism, in diabetes, especially in the comatose stage, and particularly in *scurvy*. This is a disease characterised by cachexia, spongy and bleeding gums, and subcutaneous hæmorrhages. Wright[1] regards the condition as essentially an acid intoxication.

Purpura is a condition in which there are hæmorrhages into the skin and from the mucous membranes. It may be primary, or secondary in various acute specific or other diseases, *e.g.* typhus, septicæmia, and variola, pernicious anæmia, etc. The hæmorrhage in these conditions must be regarded as being due to the action of toxic substances which render the capillary walls more permeable. The cause of primary purpura is probably an infection, but of what nature is unknown. Many drugs and snake venom also cause it.

The Chromocytes or Erythrocytes.

The normal human chromocytes are circular bi-concave discs with bevelled edges. The majority (75 per cent.) measure about 7·5 μ ($\frac{1}{3200}$ in.) in diameter, and, in the absence of a micrometer, rough measurements in microscopy may be carried out by comparison with them. Of the remainder, some 12 per cent. are a little smaller, 6–6·5 μ in diameter, and 12 per cent. are a little larger, 8–9 μ in diameter. Larger and smaller forms are occasionally met with but are very rare in health.

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[1] See *Lancet*, 1900, vol. ii, and *Trans. Epidem. Soc. Lond.*, vol. xxiii, 1904, p. 79.

The chromocytes of all mammals are non-nucleated, except in embryonic life, and are circular except in the camel, in which they are ovoid. In birds and amphibia they are ovoid and nucleated. They are soft, flexible, and elastic, and can therefore pass through channels of diameter less than themselves. The colour of a single corpuscle is a pale yellow.

The number of chromocytes averages 5,000,000 per c.mm. in men and 4,500,000 in women.

Physiological variation.—In the new-born there may be a polycythæmia, but the normal is reached in ten to fourteen days after birth. In old age there is occasionally a slight oligocythæmia. Food, menstruation, pregnancy, and lactation, provided the health be good, has little influence on the number. Persons going to, or dwelling at, high altitudes have an excessive number of chromocytes; at 6000 ft. there may be an excess of 2,000,000. Various alterations in shape may occur in drawn blood, *e.g.* spherical, spinous, crenated, and vacuolated forms.

Pathological variation.—An *increase* in number (polycythæmia) is rare and occurs only in diarrhœa and cholera, and is due to concentration of the blood—*i.e.* the increase is relative, not absolute. In certain forms of cyanosis there is also a polycythæmia. A *diminution* is common and occurs in hæmorrhage, cachexia, in the anæmias, and in leukæmia. If the number be reduced to anything approaching 1,000,000 per c.mm. the condition is serious.

Alterations in diameter and shape are frequent in disease. Small forms (*microcytes*), 3–6 μ in diameter, are common in all forms of anæmia. Large forms (*megalocytes*), 9–12 μ in diameter, are met with in severe, and especially pernicious, anæmia. *Poikilocytes*, oval and pear-shaped forms, are also present in anæmia.

Nucleated red corpuscles, erythroblasts (detected only by staining), are practically never present in normal blood but occur in severe, and particularly pernicious, anæmia. They are divided into (1) *normoblasts*, about the same size as the normal chromocytes, and having usually a single round or oval nucleus, generally excentric, and staining very deeply with nuclear dyes. They are frequent in severe and pernicious anæmias; (2) *megaloblasts*, much larger than normoblasts, 10–15 μ in diameter. The nucleus, which is large, stains much less deeply than that of the normoblast. They are met with occasionally in severe anæmia, but are a marked feature in pernicious anæmia and in myelogenous leukæmia; (3) *microblasts*, small nucleated chromocytes, met with in all forms of anæmia and not of much diagnostic significance.

Various degenerative changes may be seen in disease.

The Leucocytes.

The leucocytes are much less numerous than the chromocytes, and average 7000–8000 per cubic millimetre—*i. e.* 1 leucocyte to 600 or 700 chromocytes. Several different forms are present in normal blood, and considerable variation in number may occur in disease, in which also abnormal forms may make their appearance. The classification of leucocytes is variously given by different authors. The following normal forms may be distinguished:

(1) *Small mononuclears,* small lymphocytes, or lymphocytes, are cells 6–8 μ in diameter. They possess a single large round nucleus which stains deeply with simple basic stains, *e.g.* methylene blue or hæmatoxylin, and occupies nearly the whole of the cell. They are numerous, and constitute some 20–25 per cent. of the total leucocytes, and are non-amœboid and non-phagocytic.

(2) *Large mononuclears,* large lymphocytes, or hyaline leucocytes, are large cells 9–15 μ in diameter, with relatively more protoplasm than the small mononuclears, and the nucleus stains less deeply, and is round or ovoid in shape and often excentric in situation. They number 1–2 per cent. of the total leucocytes, and are amœboid and phagocytic (the macrophages of Metchnikoff).

Between these two varieties intermediate forms occur, not exactly conforming to either type.

(3) *Transitional forms.*—These resemble the large mononuclears, but their nuclei have a reniform or horseshoe shape.

Groups 2 and 3 comprise 2–4 per cent. of the total leucocytes.

(4) *Polymorphonuclears,* polymorphonuclear neutrophiles, polynuclears, or multinuclears, are the most numerous, constituting some 70–72 per cent. of the total leucocytes. They measure 9–12 μ in diameter, and have a lobulated, often horseshoe nucleus, sometimes apparently divided, but the portions are connected by chromatin strands. The nucleus stains deeply, the protoplasm faintly, with basic dyes. They are probably actually faintly acidophile, and are amœboid and phagocytic. Pus is almost entirely composed of this variety of leucocyte.

(5) *Eosinophiles,* coarsely granular oxyphiles or acidophiles, constitute 1–3 per cent. of the total leucocytes. They measure 10 μ or thereabouts in diameter. The nucleus is generally somewhat horseshoe-shaped, but is difficult to make out, and stains feebly with basic dyes. Their characteristic is the presence in the protoplasm of a number of large refractile granules (by which they can be distinguished unstained), which stain brilliantly with eosin and other acid dyes. They are amœboid and non-, or but slightly, phagocytic.

(6) *Mast-cells,* very scanty (0·5 per cent.) in normal blood, but abundant in the cœlomic cavity. They are large cells (20 μ) with irregular nuclei which stain faintly. The protoplasm has a number of coarse granules which are intensely basophile, and stain purplish with methylene blue, *i. e.* are metachromatic.

PHYSIOLOGICAL VARIATION.—The leucocytes are increased during intestinal digestion (digestive leucocytosis), *i. e.* three to four hours after a meal, and may reach 25–30 per cent. above the normal, *i. e.* 10,000–12,000 per c.mm. There is also a leucocytosis during pregnancy, in the new-born, and in the death agony. It is principally the small mononuclears and polymorphonuclears which are increased. Exercise, massage, and baths also raise the leucocyte count. During fasting there is a slight leucopenia.

Anything over about 10,000 leucocytes per c.mm.—*i. e.* 1 leucocyte to 500 chromocytes—may be regarded as a leucocytosis.

PATHOLOGICAL VARIATION.—A leucocytosis is a common event in the course of various diseases—*e. g.* after hæmorrhage, in inflammatory conditions and suppuration, in some fevers, in malignant disease, in certain forms of poisoning, and after certain drugs.

The occurrence of suppuration is frequently characterised by a marked leucocytosis, chiefly of the polymorphonuclears.

Tuberculin and pilocarpin, rickets, scurvy, syphilis, and whooping-cough induce a lymphocytosis.

Malignant growths of any size are usually accompanied with a leucocytosis.

In malaria the large mononuclears may rise to 8–15 per cent.

In diphtheria, myelocytes (see p. 234) may make their appearance, and, if numerous, are of bad import.

The eosinophiles are increased (*eosinophilia*) in asthma and emphysema, in pemphigus and other skin diseases, and particularly in helminthiasis—*e. g.* trichinosis and ankylostomiasis, in which they may constitute 30–50 per cent. of the total leucocytes.

In typhoid, malaria, influenza, measles, and uncomplicated tuberculosis the total leucocytes are *not* increased; in typhoid they may be diminished. Most other febrile diseases are accompanied by a leucocytosis. In all forms of leukæmia the leucocytes are enormously increased.

Glycogen may accumulate in the leucocytes, especially if suppuration be present, and in pus-cells. Little is known about variations of the *blood-platelets.*

Anæmia.

Anæmia, literally bloodlessness, includes oligæmia, oligocythæmia, and oligochromæmia. Oligæmia occurs only after hæmorrhage, or in cholera and similar conditions, and anæmia therefore usually means oligocythæmia, or oligochromæmia, or frequently a combination of these two. Anæmia is described as primary, idiopathic, or essential, or secondary or symptomatic.

Primary anæmias are those in which the condition is a primary one of the blood or blood-making organs —*e. g.* chlorosis and pernicious anæmia.

Secondary anæmias are those in which the condition of the blood is secondary to disease outside the hæmopoietic system—*e. g.* after hæmorrhage, in malaria, malignant disease, etc.

Anæmia has been classified by Hayem as of four degrees: in that of the first degree the chromocytes are reduced to 80–60 per cent., of the second degree to 60–40 per cent., of the third degree to 40–16 per cent., and of the fourth degree to below 16 per cent.

The leucocytes do not vary nearly so much as the chromocytes in the anæmias.

Chlorosis is a primary anæmia generally met with in young women, and characterised by pallor, often of a greenish tint (hence name), breathlessness, cardiac and venous murmurs, œdema about the ankles, constipation, etc. In about 40 per cent. of the cases the chromocytes do not fall below 4,000,000; in the majority of the remainder they are between 3,000,000 and 4,000,000; they rarely fall below 2,000,000 per c.mm.

The hæmoglobin is usually relatively distinctly less than the corpuscles; *e. g.* if the chromocytes number 4,000,000, the hæmoglobin will frequently correspond to only 3,000,000—*i. e.* the amount of hæmoglobin in the chromocytes is reduced; that is to say, there is a greater reduction in the hæmoglobin than in the chromocytes. The blood as it flows from a prick is often pale and watery and its specific gravity is reduced.

Microcytes and poikilocytes are common and megalocytes may appear if the anæmia be severe. In the latter case, a normoblast may be found on careful search, and in very severe cases an occasional megaloblast, but this is the exception. The leucocytes are, as a rule, but little affected; there may be a slight absolute and relative decrease. The disease is regarded as being due to deficient blood-production (hæmogenesis) the cause of which is doubtful; it has been ascribed to auto-intoxication, the result of constipation, gastroptosis, dilated stomach, etc. (but it occurs in the absence of these), to a neurosis, to vascular hypoplasia (Virchow, and the aorta is occasionally small), and to genital anomalies. Bunge has suggested a theory of iron-starvation caused by intestinal fermentation, but there is frequently no evidence of this.

Reference may now be made to some interesting observations by Lorrain Smith[1] on the volume of the blood in anæmia, etc. The method employed to estimate this was to make a patient breathe a known amount of carbon monoxide, which forms a characteristic and stable compound with hæmoglobin, and then to estimate the amount of carbon monoxide hæmoglobin in a given volume of his blood, and from this the capacity of the blood to take up oxygen and also its volume can be calculated. In normal individuals it was found that the average volume of the blood is 4·6 c.c. per 100 grams of body weight, and the average oxygen capacity of the blood is 18·5 volumes per cent., or 0·83 c.c. per 100 grams of body weight. In 21 cases of chlorosis in which the hæmoglobin per c.mm. was less than 50 per cent. of the normal, the number of c.c.'s of blood per 100 grams of body weight ranged from 7·3 to 14·3, averaging 10·8, more than double the normal, and the oxygen capacity averaged 0·79 c.c. per 100 grams of body weight—*i. e.* about 95 per cent. of the normal. The volume of the blood increased *pari passu* with the severity of the anæmia. Therefore, so far from there being a decrease in the number of chromocytes there is absolutely an *increase*, but since the volume of the blood is increased to a greater extent, there is an apparent or relative diminution in the chromocytes. Similarly, there is a slight or absolute increase in the leucocytes, chiefly in the lymphocytes. The cause of the increase in the volume of the blood is unknown, but it explains many of the symptoms of the disease. As Lorrain Smith points out: "The fact that such a large volume of blood has to be sent through the vessels in one round of the circulation throws greatly increased work on the heart, and diminishes the value of any given quantity of the blood for respiratory exchange. We may in this way explain the quick action, as well as the hypertrophy and dilatation, of the heart which occurs in many cases of chlorosis. Similarly, we may hope to obtain some light on the controversy as to the cause of the functional cardiac murmurs which are so frequently present in anæmia. The suggestion arising from the results is that the increased volume of fluid leads to an abnormal tension of the valves and vessel walls, especially during the active propulsion of the beat."

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[1] *Path. Soc. Trans.*, vol. li, 1900, p. 311.

These results also offer an explanation of the "dyspnœa which is another characteristic of chlorosis. While the blood as a whole has a normal capacity for oxygen, the increase in quantity renders it unwieldy as an oxygen carrier. Further, the dyspnœa may be due in some measure to the overloading of the blood with carbonic acid. The action of aiding in the expulsion of carbonic acid from the blood in the lungs, which has been ascribed to the hæmoglobin, will be reduced; consequently the blood may leave the lungs without being sufficiently freed from the carbonic acid in the plasma."

PERNICIOUS ANÆMIA.—Progressive pernicious anæmia is a disease (or complex of diseases) occurring chiefly in middle life and is more frequent in males than in females in the proportion of 3 to 2. It is characterised by progressive anæmia, breathlessness, asthenia, and the occurrence of hæmorrhages from mucous membranes and into the retina, and almost always ends fatally, though there are frequently periods of improvement during its course. The patients are generally well nourished, and have a peculiar lemon-coloured tint of skin and conjunctivæ.

The blood in most cases is thin and watery, very fluid, coagulates slowly, and the specific gravity is much diminished—*e. g.* to 1025.

The chromocytes are reduced to 3,000,000 – 1,000,000, and before death often to less, per c.mm. The hæmoglobin is also absolutely decreased, but relatively usually not to such an extent as the corpuscles—*i. e.* the amount of hæmoglobin per corpuscle is increased, a contrast to what obtains in chlorosis. Microcytes and poikilocytes are plentiful, and megalocytes are generally numerous. Rouleaux formation is absent or slight, and the chromocytes, instead of taking up only the eosin when stained with hæmatoxylin and eosin, frequently have their affinities altered and take up both dyes, so that they appear purplish.

Erythroblasts as a rule are a prominent feature. Normoblasts and megaloblasts are both present (Plate XI., A.), but the latter usually preponderate in about the proportion of 4 : 1 (contrast with severe chlorosis, p. 227). In fact, briefly to sum up the characters of the blood in pernicious anæmia, it may be said to be megalocytic and megaloblastic. There does not seem to be any marked correspondence between the number of erythroblasts and the severity of the disease; in the remissions of the disease, however, the nucleated forms tend to disappear. A decided diminution in the leucocytes is the rule, and they may be as low as 1000 per c.mm.; a few myelocytes are frequently present. Now and then leucocytes are seen with chromocytes in their interior.

Important changes are also present in the bone-marrow and various organs. The bone-marrow is occasionally unaltered, but usually the yellow fatty marrow of the long bones becomes transformed into red marrow, and microscopically a number of megaloblasts can be detected.

Fatty degeneration of the kidneys, liver, and particularly of the heart generally occurs; the gastric and intestinal mucous membrane is atrophic; hæmorrhages occur in the organs, serous membranes, and retina, and from mucous surfaces; iron is present in large excess in the liver and to a less extent in the kidneys and spleen, and urobilin is excreted in excess in the urine. Lastly, degeneration of the posterior columns of the cord in the dorsal and cervical regions is nearly always present. The spleen and lymphatic glands show little or no change.

In contrast to chlorosis (see *ante*, p. 228), Lorrain Smith finds that the *total* amount of hæmoglobin is reduced in proportion to the severity of the disease; the volume of the blood may be increased or reduced.

The causation of the disease is quite obscure, and has been attributed to various conditions—pregnancy, fevers, hæmorrhage, intestinal parasites, gastric atrophy, etc.—but these are probably simply antecedents. Oral sepsis and septic gastritis and enteritis are regarded by Hunter and many others as important causes.

Infection with the tape-worm *Dibothriocephalus latus* produces an anæmia which is accepted by Lazarus and others as a pure picture of pernicious anæmia, and from tape-worms a toxic substance having hæmolytic properties has been extracted. Ehrlich and Lazarus therefore regard the pathogenesis of the disease as due to the presence of hæmolytic substances, and the changes in the bone-marrow and blood as a reaction of stimulation and an attempt at repair. The hæmolytic substances may be the result of gastro-intestinal infection.[1]

Hunter[2] believes that under the name "pernicious anæmia" two classes of affections have been grouped. One, which he terms "septic anæmia," he regards as a heterogeneous collection of anæmias comprised within Biermer's definition of "progressive pernicious anæmia," and the other, "infective hæmolytic anæmia" or Addison's "idiopathic anæmia," as a specific infective hæmolytic disease due to infection of the gastric and intestinal mucous membrane with a streptococcus. The septic anæmia arising in connection with oral and other sepsis, according to Hunter, is characterised by the presence of normoblasts and occasionally of megaloblasts, absence of bone-marrow changes, and of an excess of iron in the organs, and favourable course if the cause be removed. The infective anæmia is characterised by intense hæmolysis and pigmentary changes and presence of iron in the organs, with bone-marrow, and more marked blood-changes, the occurrence of a peculiar glossitis, which is connected with exposure to drain poisons, and a streptococcic infection of the mucosa of the tongue, mouth, stomach, and intestine.

SPLENIC ANÆMIA.—This is a condition in which the spleen is enlarged, often enormously so. An anæmia of the chlorotic type is present, but the leucocytes are normal, or there may be some leucopenia. Hæmorrhages occasionally occur and the liver may be slightly enlarged. The disease is usually chronic, but acute cases have been recorded. The ætiology is unknown.

Chronic cyanotic polycythæmia, a condition described by Osler,[3] is characterised by intense cyanosis, considerable enlargement of the spleen, and a blood-count of 6,000,000–10,000,000 chromocytes per c.mm. He regards it as being due to increased specific gravity and viscosity (? diminished volume) of the blood.

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[1] See a good summary on this disease by Bunting, *Johns Hopkins Hospital Bull.*, No. 171, 1905, p. 222.

[2] See *Brit. Med. Journ.*, 1904, vol. ii, p. 1358.

[3] *Brit. Med. Journ.*, 1904, vol. i, p. 121.

Leukæmia.

Leukæmia, or leucocythæmia, is a condition characterised by the presence of enormous numbers of leucocytes in the blood and in the organs. Three forms of the disease are generally recognised—(1) the chronic myelogenous, (2) the chronic lymphatic, and (3) the acute lymphatic, though there is often a blending of the first two. All tend to a fatal issue. The pathogenesis of the disease is unknown, and no cause can be assigned to it. Some stimulus excites the abnormal production of leucocytes, but what this is we do not know; it may be an infective agent, but none has been isolated. By some the disease has been regarded as malignant, a kind of "fluid" sarcoma. It is probably an affection of the blood-making organs rather than of the blood itself, since leucocytes showing mitosis are almost exclusively found in the organs and not in the blood.

The blood may be of normal colour, or may be pale, or occasionally milky. The leucocytes may range from 100,000 up to 500,000 or more per c.mm., and the ratio of white to red corpuscles, instead of being 1 to 600, is frequently 1 to 8, but may reach 2 to 3 or even 2 to 1. In the milder cases, the quality of the leucocytes is of greater importance than their quantity (and this can be brought out only by staining), since cases of leucocytosis do occur up to 70,000 leucocytes per c.mm.

A curious fact is that an intercurrent attack of febrile disease is often attended with a marked decrease in the number of the leucocytes. Treatment is usually of little permanent benefit, but recently X-ray treatment has been found speedily to bring about a reduction in the number of leucocytes,[1] and to produce an extraordinarily beneficial effect.

Anæmia is frequently, but not necessarily, present, and hæmorrhages from mucous membranes are common. Œdema, ascites, diarrhœa, etc., occur.

Febrile attacks are common during the course of the disease, the uric acid excretion is much increased, and leucin, tyrosin, xanthin, adenin, etc., may appear in the urine and in the spleen and liver.

MYELOGENOUS LEUKÆMIA, chronic myelocythæmia, or spleno-medullary leukæmia, is the form most frequently met with. The leucocytes are enormously increased, the striking feature being the appearance of numbers of *myelocytes* or marrow-cells. These are large non-amœboid cells 10–20 μ in diameter, having a large rounded, oval, or slightly indented, often excentric, nucleus staining faintly with nuclear dyes, with a fair amount of cytoplasm containing very fine granules and described as neutrophile or faintly acidophile. This is the common type of cell found in red marrow, and it constitutes 30–60 per cent. of the total leucocytes in this form of leukæmia (Plate XI., B.).

Eosinophiles are also generally in excess, some being of the normal type, others of the myelocyte type, but containing eosinophile granules (eosinophile myelocytes). The *small mononuclears* are generally relatively reduced to 5 per cent. or thereabouts, but are absolutely slightly increased in numbers. The *large mononuclears* are usually relatively diminished, while the *polymorphonuclears* are absolutely largely increased though relatively diminished in numbers. Most cases also show cells (2–6 per cent.) with basophile granules, finely granular (δ) basophiles, and particularly coarsely granular large basophiles which seem to be identical with mast-cells.

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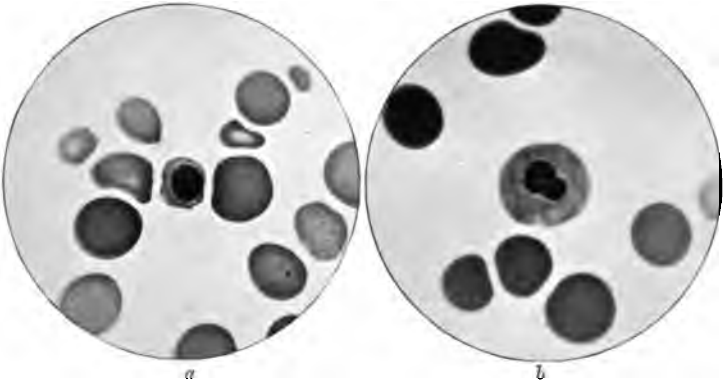
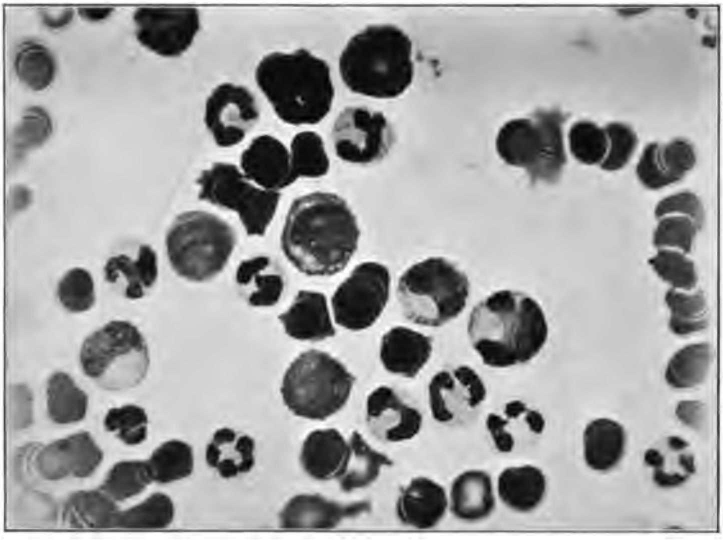
[1] See W. I. Bruce, *Lancet*, 1906, vol. i, p. 211.

PLATE XI.



A. Blood-films from a case of pernicious anæmia. A normoblast is shown in the left-hand figure, *a*, and a megaloblast in the right-hand figure, *b*. (Hæmatoxylin and eosin, × 1000.)



B. Blood-film from a case of myelogenous leukæmia. Several polymorphonuclear leucocytes and myelocytes are shown. (Hæmatoxylin and eosin, × 1000.)

The *chromocytes* at first are not reduced nor is there oligochromæmia. Later they become reduced and also the hæmoglobin proportionately, but the patients are rarely pallid. Microcytes, poikilocytes and megalocytes may make their appearance, and normoblasts and megaloblasts are a constant feature.

The *spleen* is enormously enlarged, its consistency is increased from hyperplasia of the fibrous stroma, and it is paler than normal, frequently adherent, and hæmorrhage into, or rupture of, it may occur. Microscopically the fibrous tissue is much increased, the Malpighian bodies are obscured, and although the majority of the cells are lymphocytes, relatively to a normal spleen, these cells are considerably reduced, and myelocytes, mast-cells, and polymorphonuclears are numerous. The *liver* is generally much enlarged, infiltrated with leucocytes, and the capillaries are much dilated and form a striking feature. Leucin, tyrosin, xanthin, etc., can be extracted from the spleen and liver and Charcot-Leyden crystals are often present. The *bone-marrow* is hyperplastic and myelocytes are increased. The *lymphatic glands* are as a rule slightly enlarged. The enlarged abdominal organs may displace the heart and may cause ascites, intestinal obstruction, etc.

LYMPHATIC LEUKÆMIA, or chronic lymphæmia, is much rarer than the myelogenous form and more acute in its course. The leucocytes are practically all of the *small mononuclear* type, constituting 95–98 per cent. of the total. The *large mononuclears* correspond with those of normal blood, the *polymorphonuclears* are absolutely and relatively diminished, and *eosinophiles* are very scanty. *Myelocytes* are occasionally present in very small numbers. The chromocytes may be diminished and an anæmia of a secondary type be present, but, unless extreme, nucleated chromocytes are absent.

The *spleen* and *liver* as a rule are only slightly enlarged. Many, or all, of the lymphatic glands may be much enlarged, and the cellular infiltration that is present in the organs mentioned is composed of lymphocytes, which in some cases form metastatic nodules, or *lymphomata* (rare in myelocythæmia), which may be widespread in the organs and tissues. The *bone-marrow* is generally hyperplastic and infiltrated with lymphocytes, which crowd out the normal cells.

CHLOROMA[1] is a remarkable and rare disease, which in typical cases is characterised, according to Byrom Bramwell, by the following features:

(1) The presence of lymphoid deposits in the orbits, temporal fossæ, and periosteum of the bones of the skull, and the symptoms and signs arising therefrom.

(2) The green colour of the lesions.

(3) A profound blood change, of which the characteristic feature seems to be an enormous excess of lymphocytes.

(4) The bone-marrow, spleen, lymphatic glands, and organs throughout the body are affected (infiltrated with lymphoid deposits) as in lymphatic leukæmia.

ACUTE LEUKÆMIA, or acute lymphæmia, usually occurs between the ages of 11 and 25, and may progress to a fatal issue in the course of a few weeks, and, although chronic lymphæmia may have an acute terminal stage, the blood-picture in the two diseases is distinctly different. The leucocytes are not so numerous as in the other two varieties, rarely exceeding 100,000 per c.mm., and consist mainly of the small mononuclears as in the chronic lymphæmia. A large proportion of them are pale and show degenerative changes—*e. g.* are swollen with vacuolated nuclei, or the nucleus has only fragments of cytoplasm around it. Instead also of being mainly of the small forms with dark-staining nuclei, as in the chronic lymphæmia, many are large—

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[1] See Hichens, *Brit. Med. Journ.*, 1903, vol. ii, p. 1632.

i. e. of an intermediate type. The large mononuclears remain much the same as in normal blood, but the polymorphonuclears and eosinophiles are much reduced, or disappear. The red corpuscles are much reduced, and a few erythroblasts may make their appearance—in this respect the blood in acute lymphæmia is intermediate between chronic myelocythæmia and chronic lymphæmia. Hæmorrhages are usually a marked feature and may occur in the skin, mucous and serous membranes, and organs. The lymphatic glands are slightly, and the spleen somewhat, enlarged; both are often soft. Metastatic lymphomata are numerous and widespread. Changes in the bone-marrow occur.

Pseudo-leukæmia infantum is the name applied by von Jaksch to a form of lymphocytosis with enlarged spleen and liver occurring in children. There is also oligocythæmia, and leucocytes of all forms are present. The disease seems to be related to rickets and congenital syphilis.

THE SPLEEN.

The spleen is enclosed within an elastic fibrous capsule containing smooth muscle, and hence considerable alterations in its volume are possible and occur physiologically. From the capsule, trabeculæ pass inwards and with a network of retiform tissue form interspaces containing the fairly large polygonal splenic cells and leucocytes. The blood-vessels are beset in their course along the trabeculæ with small masses of lymphoid tissue, the Malpighian bodies, and become discontinuous, so that the blood is poured out into the interstices of the tissue. The spleen is one of the seats of formation of lymphocytes; it probably does not form chromocytes, and is the great blood-filter where effete red and white blood-cells are broken down, in consequence of which it contains pigment and much extractive matter, leucin, xanthin, uric acid, etc. The spleen is not essential to life. Its size varies, averaging 12–14 cm. in length, 2·5–4 cm. in thickness, and 8–10 cm. in breadth, and weighs 150–200 grms.

Anomalies and displacements.—Complete absence of the spleen is of the rarest occurrence. It may be present as multiple scattered masses (splenunculi), and these may occur in addition to the normal gland; lobulation is sometimes observed. It may be transposed with the other viscera, and at times is movable and may be associated with gastroptosis, etc.

Enlargement of the spleen occurs from active hyperæmia in acute infective diseases and in inflammation, from passive hyperæmia in chronic cardiac and pulmonary diseases, and in cirrhosis of the liver. In infarction, abscess, lardaceous disease, tumours, parasitic cysts, rickets, and myelogenous leukæmia, the spleen is enlarged. The greatest enlargement occurs in malaria (p. 143), kala-azar (p. 140), myelogenous leukæmia (p. 234), lardaceous disease, abscess, and sarcoma.

HYPERÆMIA.—Active hyperæmia is most frequently seen in acute infective diseases, in most of which—*e. g.* typhoid and septicæmia—a moderate enlargement of the spleen is present. The spleen is engorged with blood, soft and pulpy. Passive hyperæmia occurs in chronic cardiac valvular disease, emphysema, etc., and in hepatic cirrhosis. The spleen is enlarged, firm, and dark red, and if the condition has lasted for some time, may be very hard and tough from fibrous hyperplasia.

INFARCTION is frequent, and usually results from plugging of a branch of the artery by an embolus derived from the left heart or aorta. Occasionally the splenic artery or vein may be thrombosed. The infarcts may be either hæmorrhagic or anæmic, single or multiple, and vary in size from a mere point to half the organ, and eventually become converted into pale, fibrous cicatrices. Infective emboli speedily terminate in abscess. Thrombosis of the splenic artery or vein causes total necrosis.

Hæmorrhage occurs from traumatism or infarction.

Inflammation, acute splenitis, non-suppurative, occurs in the course of infective diseases. The organ is enlarged and softened, the vessels dilated, and infiltration with round cells is marked. It usually terminates in recovery.

Purulent splenitis most frequently occurs in the course of some septic process—pyæmia, infective endocarditis, etc. It may also arise by extension, as from gastric ulcer.

Chronic interstitial splenitis, a condition of diffuse hyperplasia of the connective tissue, results from repeated attacks of acute splenitis as in malaria, from venous congestion as in hepatic cirrhosis, and from syphilis. The capsule is thickened and adherent, and the fibrous tissue everywhere increased, together with pigmentary infiltration (*cyanotic induration*).

Lardaceous disease may be diffuse, affecting the vessels of the pulp, or usually attacking the vessels of the Malpighian bodies, converting these into greyish translucent bodies like grains of sago, the *sago spleen.* It generally occurs in the course of prolonged suppuration or in syphilis.

Tuberculosis occurs as a miliary infection in general tuberculosis, or sometimes as chronic caseating masses.

Syphilis may cause a diffuse fibrous hyperplasia, or rarely gummata may be formed. Lardaceous degeneration is another result of syphilitic infection.

Tumours.—Carcinoma is rare and always secondary.

Sarcoma is also rare and generally secondary, occasionally primary. Lymphomata have been mentioned in connexion with lymphatic leukæmia (p. 236). Hydatid cysts have been met with.

THE LYMPHATIC GLANDS.

The lymphatic glands may undergo atrophy in wasting diseases and in old age. Pigmentation is common, the pigment being carried by the lymphatic vessels and intercepted in the glands. It occurs after hæmorrhage, in malaria and Addison's disease, after tattooing, and in the bronchial glands in miners and others who inhale particles (see Pneumokoniosis). Calcareous infiltration is common in tuberculous disease, and lardaceous infiltration is sometimes present in chronic suppuration, the blood-vessels and trabeculæ being the parts affected, not the lymphoid cells, except by compression. Enlarged lymphatic glands in the groin and axilla are frequently spoken of as "buboes."

Lymphadenitis, inflammation, may be acute or chronic. *Acute lymphadenitis* is generally due to some infection, local as in sepsis—*e. g.* the glands in the groin become infected from a foul wound of the foot, in the neck from carious teeth, etc.—or general as in plague, scarlatina, diphtheria, etc. The glands become hyperæmic, enlarged, and tender, and microscopically the vessels are dilated, hæmorrhages may be present, round-celled infiltration is marked, and the lymph-sinuses are filled with desquamated endothelial cells and leucocytes. Suppuration often occurs, especially in connection with sepsis, in gonorrhœa, and in chancroid. *Chronic lymphadenitis* may be a sequel of the acute form, or may be chronic from the first and result from the continuous operation of septic material which is not of sufficient intensity to set up the acute process, or it may be caused by tubercle or syphilis. There is more or less increase in the fibrous tissue. Frequently the tissues surrounding the gland partake in the inflammatory process—*periadenitis.* *Tuberculous lymphadenitis* is caused by infection with tubercle bacilli conveyed by the lymphatic vessels or, rarely, by the blood. The cervical, mesenteric, and bronchial glands are those most commonly affected. Usually the process is a chronic caseating one, terminating in suppuration. Microscopically, giant cells and endothelioid cells are well marked and are surrounded with a round-celled infiltration. Tubercle bacilli are scanty. In some instances the cells are almost exclusively endothelioid in type (large-celled indurative hyperplasia of Ziegler).

Syphilitic lymphadenitis occurs in the neighbourhood of the primary lesion. There is a considerable infiltration with leucocytes, and fibrous hyperplasia may ensue. In the tertiary stage gummata may occur.

Elephantoid lymph-glands are met with in the groin in filariasis. They are usually painless, though subject to attacks of lymphadenitis, and contain a milky fluid in which the filariæ may be detected. Anatomically the condition is a lymph varix.

TUMOURS of the lymphatic glands may be primary or secondary. All tumours which give rise to metastases may affect the lymphatic glands. Carcinoma is particularly liable to form secondary growths in the glands, the structure of the primary tumour often being faithfully reproduced (see Plate IV., B.). Sarcomatous metastases may also occur. Of the primary tumours, some have the character of normal lymphadenoid tissue, in others the normal tissue is displaced by tissue of a different kind. The former group includes the lymphoma, lymphadenoma, and lympho-sarcoma, the latter various forms of sarcoma.

The *lymphoma* is characterised by the formation of nodules of lymphoid tissue, and occurs most frequently in lymphatic leukæmia.

In the *lympho-sarcoma* the lymphadenoid structure is preserved, the cells being increased and the reticulum thickened. A hard and a soft form have been described. Histologically, it is almost impossible to distinguish between a hyperplasia and a sarcomatous metamorphosis.

LYMPHADENOMA.—A disease of unknown ætiology, possibly parasitic, and characterised by enlargement of the lymphatic glands (which remain discrete) and other lymphoid structures of the body, the blood, however, being normal or showing the changes of a secondary anæmia only; there is no leucocytosis unless towards the close, when there may be some increase in the polymorphonuclears. If the enlargement is limited to a few of the glands, it is generally termed lymphadenoma, and may be benign, but frequently the glands more or less throughout the body are involved as well as the lymphoid tissue of the liver and intestine, and the spleen may be much enlarged and studded with lymphoid nodules. This form usually progresses to a fatal issue, and has been variously termed Hodgkin's disease, lymphoma, lymphadenoma, lympho-sarcoma, pseudo-leukæmia, etc. By some it has been supposed to be a pre-leukæmic stage of leukæmia, but there is little evidence in support of this. According to Andrewes,[1] the true Hodgkin's disease is characterised by the following changes in the glands: (1) The general plan of the structure of the gland is obscured and simplified, the distinction between cortex and medulla is abolished, or nearly so, so that the whole gland has a more homogeneous appearance. (2) The number of lymphocytes is apparently very much decreased; they are proportionately scanty, and no longer conceal the supporting framework of the gland. (3) In correspondence with this, the framework has undergone hyperplasia, the fibrillar reticulum is conspicuous —its increase may amount to an actual fibrosis. The endothelial cells in connexion with it are more numerous and much more evident; here and there some of them attain a very large size, and may contain two, four, or more large and deeply stained nuclei (see Pl. XII., A.). These are the cells especially characteristic of lymphadenoma described by Virchow, and I think an endothelial origin may fairly be ascribed to them. They are especially numerous in the soft, rapidly-growing forms of the disease; they are not always uniformly distributed, but sometimes occur numerously at special places, and I have been able to demonstrate large and beautiful karyokinetic figures in them. They may properly be called "lymphadenoma cells," and though they are large, multinucleate cells, they have little resemblance to the giant cells met with in tubercle. They are not so large as the latter, they are more rounded, and their nuclei, fewer in number, are larger, stain more deeply, and occupy a more central position; their protoplasm has less tendency to degenerative changes. They most nearly resemble the large cells found here and there in many rapidly growing sarcomas. (4) The eosinophile cells present in normal glands are always demonstrable in lymphadenoma, sometimes, but not always, in vastly increased numbers.

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[1] *Path. Soc. Trans.*, vol. liii, 1903, p. 306.

The disease has no relation to tuberculosis, though tubercle may be engrafted on it (see Andrewes, *loc. cit.*), and doubtless tuberculous and syphilitic glandular enlargements have sometimes been confounded with lymphadenoma.

Sarcoma of the lymphatic glands is uncommon; it may be of the round- or spindle-celled, or occasionally of the alveolar, type.

Status lymphaticus, lymphatism, is a condition occurring chiefly in children and the young, in which the lymph-glands and lymph-tissue throughout the body, the spleen, thymus, and bone-marrow, are in a state of hyperplasia. Attention has been directed to the condition by the frequency with which it has been found in cases of sudden death from trifling and inadequate causes[1] (see also p. 207).

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[1] See Osler's *Text-Book of Medicine*, 5th ed., p. 826.

CHAPTER XII.

PATHOLOGICAL VARIATIONS IN THE DISTRIBUTION OF THE BLOOD WITHIN THE VESSELS—HÆMORRHAGE—THROMBOSIS —EMBOLISM.

PATHOLOGICAL VARIATIONS IN THE DISTRIBUTION OF THE BLOOD WITHIN THE VESSELS.

THE quantity of blood in the body is insufficient completely to fill all the vessels at the same time, and the amount of blood in an organ or tissue varies with its activity. The regulation of the blood-supply is carried out by changes in the calibre of the arteries, chiefly of the medium-sized ones or arterioles, whose walls are plentifully supplied with smooth muscle-fibres which contract or relax under impulses from the vaso-motor centres. When filled with blood an organ or tissue is said to be *hyperæmic*; when containing little blood it is said to be *anæmic*. Should the quantity of blood vary above or below these physiological limits, a pathological hyperæmia or anæmia results.

Hyperæmia may be arterial or active, or venous or passive.

ACTIVE OR ARTERIAL HYPERÆMIA, congestion, may be due to paresis of the vaso-constrictor nerves, or stimulation of the vaso-dilators, both of which events cause relaxation of the muscular tissue of the arteries, or to direct weakening or paralysis of the muscular coat of the arteries, as by heat or traumatism. A collateral hyperæmia occurs when the blood supply to some other part is diminished. Thus if an artery be blocked, the area supplied by it will be anæmic, and around this a zone of hyperæmia will for a time be present.

PASSIVE HYPERÆMIA, engorgement, arises from interference with the venous outflow from a part. This may be due to various factors. The venous circulation is mainly carried on by the contraction of the muscles and by the aspiration towards the thorax which occurs during inspiration. If these forces fail, the blood stagnates in the veins and especially collects in the most dependent parts. The term "hypostasis" is sometimes erroneously applied to this condition, but should be reserved for the post-mortem gravitation of the blood.

The causes of general passive hyperæmia are enfeebled heart's action and uncompensated valvular disease, of local passive hyperæmia, the interposition of an abnormal resistance in the course of the veins; the latter may be caused by external compression by tumours, by occlusion of the lumen by growths, thrombosis, contraction of scar-tissue, etc., by increased pressure in the abdomen by the pregnant uterus, tumours, and the like. If there be free anastomosis in the region supplied by the occluded vein, the hyperæmia subsides as soon as the collateral circulation becomes established, but if this does not occur the engorgement will persist, as is the case when such veins as the splenic, the renal, the portal, and the sinuses of the dura mater, are occluded.

In the systemic circulation the engorgement is confined to the veins and capillaries, the arterial pressure remaining unaffected, but in the pulmonary vessels the engorgement is propagated backwards through the arteries to the right heart and there causes increased pressure.

If a part be observed in which venous obstruction has been induced (*e. g.* by ligature of the lingual vein at the root of the frog's tongue) the blood-current slows and finally ceases—*stasis*—the veins and capillaries dilate and become crowded with closely-packed red corpuscles, a few of which may make their way out of the vessels into the surrounding tissues—*diapedesis*—and the plasma seems to have disappeared, an increased quantity having transuded into the tissues. Hyperæmic tissues are swollen and œdematous, if congested hot and bright red in colour, if engorged cold and purplish, or livid.

Anæmia, literally "bloodlessness," is used in various senses. There may be *oligæmia*, a general deficiency of blood throughout the body, or *ischæmia*, diminution in the blood-supply of a part. Local anæmia or ischæmia may be caused by narrowing or occlusion of the lumina of the arteries supplying a part, by pressure from without by tumours, cicatricial contraction, inflammatory exudation, etc., alterations in their walls by endarteritis, etc., formation of thrombi or lodgment of emboli (see p. 254), or by vasomotor constriction. The last-named may be induced by cold, and occurs idiopathically in Raynaud's disease. A hyperæmic area is frequently surrounded by a zone of collateral anæmia. Anæmic parts are pale and cold.

When a main artery is occluded an increased flow soon follows in the neighbouring anastomosing branches; these become larger, and the capillaries dilate and gradually acquire the structure of arteries, so that the circulation before long becomes completely re-established. Deprivation of arterial blood sets up a condition in the part whereby the vessels supplying it in some way dilate ready to receive any fresh arterial blood which may come to it. This adjustment is not altogether dependent on vasomotor influences. The results of the occlusion of vessels by thrombosis and embolism will be described later (pp. 258 and 263).

HÆMORRHAGE.

The escape of the blood (all its constituents) from the vessels is known as *hæmorrhage.* It may occur on a free surface or into the tissues, from the cavities of the heart, or from the arteries, veins, or capillaries. Small hæmorrhages into the skin are known as *petechiæ* or *ecchymoses*; if the blood forms a tumour this is known as a *hæmatoma.* Bleeding from the nose is *epistaxis,* from the stomach *hæmatemesis,* from the lungs *hæmoptysis,* from the bowel *melæna,* from the urinary organs *hæmaturia,* from the uterus *metrorrhagia* if irrespective of the menstrual flow, while excessive menstrual flow is *menorrhagia.* A collection of blood in the pericardium is *hæmopericardium,* in the pleural cavity *hæmothorax,* in the tunica vaginalis or Douglas's pouch *hæmatocele,* in the uterus *hæmatometra.* Hæmorrhage into an organ is termed an *apoplexy.*

Hæmorrhage may take place in two ways, either by solution of continuity, *rupture* or *rhexis,* or, from the smaller veins and capillaries, by *diapedesis.*

Hæmorrhage by rupture may be either traumatic or spontaneous. The latter occurs in consequence of a rise of blood-pressure acting on diseased vascular walls. It is generally admitted that healthy fully-developed arteries and veins are never ruptured by any increased intra-vascular pressure to which they may be subjected, though healthy capillaries may be so ruptured. The morbid changes which diminish the strength of the vascular walls are inflammation and sclerosis, fatty degeneration, and aneurysm, and the effects of inflammation and morbid growths around them. Loss of support may also be the essential cause, as in phthisical cavities.

Diapedesis occurs as the result of some local circulatory disturbance, particularly the occlusion of a vessel by thrombosis or embolism, and frequently accompanies infective processes, as in septicæmia and pyæmia, fevers, etc. If a vein in a frog's tongue be tied and the subsequent changes watched, it will be found that first of all stasis of the blood occurs, then the small veins and capillaries become packed with corpuscles, which after a time pass out of the vessels and accumulate in the tissue spaces. At one time it was supposed that definite openings or stomata are present in the vessel walls; but it is now considered that the permeability of the vessel walls is increased owing to loosening of the cement substance between the endothelial cells, and that the blood-corpuscles are pushed through these relatively soft spots by the rise in intra-capillary pressure, much in the same way as a solid body will pass through a jelly without leaving an appreciable aperture (see also below). Hæmorrhage by diapedesis may reach a considerable extent. The results of hæmorrhage vary much with the rapidity of the hæmorrhage. Within limits, the circulatory organs are able to adjust themselves to compensate for the loss of blood. A rapid hæmorrhage may quickly prove fatal from fall of blood-pressure and cerebral anæmia, while much more blood may be lost without fatal result if the hæmorrhage be slow and gradual. In the latter case the arteries contract and so keep up the blood-pressure in spite of the loss of blood, while fluid is absorbed from the tissues and also helps to compensate for the loss. It has been calculated that half the total blood may be slowly lost by hæmorrhage without material fall in aortic pressure. In extensive hæmorrhage it is more the loss of fluid in the vessels and fall in blood-pressure than the actual loss of the constituents of the blood which is the serious event, and hence the utility of saline infusion in the treatment of hæmorrhage. During hæmorrhage, the coagulability of the blood increases and favours thrombosis and the arrest of the hæmorrhage. The danger of hæmorrhage also varies with its site. Thus a small hæmorrhage into the pericardial sac may so impede the heart's action as to cause death, into the brain may interfere with the action of vital centres, and so on.

The extravasated blood in a tissue or organ after the cessation of the hæmorrhage undergoes various changes. If small, it may become infiltrated with leucocytes and completely removed, but more usually a fibrous cicatrix remains. Various degrees of softening may also occur and cyst-formation, particularly in the brain, may ensue. The hæmoglobin undergoes changes, first into hæmatin, then into hæmatoidin, which is iron-free and very similar to bilirubin, and also into hæmosidiren (which contains iron), etc., and the ultimate brownish *débris* that may remain consists largely of iron sesquioxide. The transformed pigments are partially reabsorbed and finally excreted in the urine as urobilin. These changes in the pigments are coincident with the colour changes so well seen in the skin, first brown, then blue and green, and lastly yellow. Hæmatoidin crystals form reddish rhombic tablets or needles and are frequently found in the remains of old blood-clot.

Post mortem, the blood-corpuscles may break down and the hæmoglobin be dissolved and stain the vascular endothelium. This solution of the blood-corpuscles (*hæmolysis*) and discharge of hæmoglobin is seen in various infective diseases and is due to bacterial or other toxins. Poisoning with acids may also cause hæmolysis. In certain individuals there is a great tendency to hæmorrhage on the slightest provocation; this is known as *hæmophilia,* or the hæmorrhagic diathesis, and the subjects of it are termed *bleeders.* The cause of this abnormality is not known with certainty; there may be an inherent defect in the vascular walls, and there is frequently a deficiency of calcium salts in the blood, with diminished coagulability. Hæmophilia is markedly hereditary and is transmitted through the females; though the daughters of a "bleeder" father may not suffer from the disease, they transmit it to several of their offspring, both male and female. Hæmorrhages are the most prominent symptom of certain diseases, notably scurvy and purpura, and may also occur after poisoning, *e. g.* with snake-venom and phosphorus, and in many infective diseases—septicæmia, smallpox, typhus—and in these cases generally indicate a severe or "malignant" form of the disease. Other diseases may also be accompanied by hæmorrhages, particularly pancreatic affections, also leukæmia and nephritis. In all these cases alterations in the capillary walls must be regarded as the cause of the hæmorrhages.

Recent observations by Flexner[1] and others on hæmorrhage by diapedesis, such as occurs, for example, in poisoning by ricin or by snake-venom, have shown that there is no need to assume hypothetical molecular alterations in the vessel walls. In the smaller veins and capillaries distinct bulgings and irregular dilatations may be seen, and it is probable that in many of them actual rents in the vessel walls are present. Flexner suggests that these are due to solution of the vascular endothelium by a substance termed "hæmorrhagin," which may be regarded as a cytolysin for endothelial cells of blood-vessels, and doubtless similar endotheliolysins may be produced by many micro-organisms and are the cause of the hæmorrhages so frequently met with in certain infections.

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[1] See *Amer. Journ. of Med. Sci.*, August, 1903.

THROMBOSIS.[1]

A thrombus is usually defined as a blood-coagulum formed in the heart or vessels during life, and thrombosis is the process of formation of a thrombus, though some deny that *all* thrombi are genuine coagula (Welch).

Thrombi are described as red, white, or mixed. Occasionally thrombi may consist wholly of leucocytes, of fibrin, or of hyaline material.

Red thrombi are formed in stagnating blood and have practically the same structure as an ordinary blood-clot—*i. e.* a fibrillated fibrin entangling red corpuscles and leucocytes. Where exposed to the circulating blood a whitish layer becomes deposited on the thrombus, and may serve to distinguish a thrombus from a post-mortem clot.

White and *mixed thrombi* are formed from the circulating blood, and are white or grey, or mixed red and white in colour. They consist of fibrin, blood-platelets, and leucocytes, with but few red corpuscles. Microscopically, a white thrombus consists of interlacing strands of fibrin, entangling leucocytes, and a larger or smaller number of red corpuscles and islands of granular detritus. This granular detritus is now considered to be the essential part of the white thrombus, and to consist of altered blood-platelets.

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[1] On Thrombosis, see an exhaustive article by Welch in Clifford Allbutt's *System of Medicine*, vol. vi, p. 155.

The earlier view of the formation of a thrombus was that the process is initiated by the collection of leucocytes, which on breaking down led to the formation of fibrin and a clot. The general opinion now is that the first step in thrombosis is the accumulation of blood-platelets which coalesce and form plugs ("conglutination"); leucocytes of the polymorphonuclear variety next rapidly increase in number and collect at the margins of the platelet masses and then fibrillated fibrin makes its appearance.

In the smaller vessels and capillaries in inflamed areas, thrombi, composed wholly of polymorphonuclear leucocytes or of fibrin, are occasionally seen (Welch), and in certain infective processes hyaline thrombi may similarly occur. The thrombus at its commencement forms a coating on the walls of the vessel or heart (mural thrombus), but by continued growth may fill the vessel and become an occluding thrombus. A secondary thrombus is one forming around an embolus; loose thrombi in the heart are known as ball-thrombi. A thrombus frequently grows in length, generally in the direction of the blood-stream. The larger thrombi are usually stratified, layers of white and red alternating, and their free surfaces are frequently ribbed, a structure which has been ascribed to the wave-like motion of the flowing blood.

CHANGES IN THROMBI.—In old thrombi various changes may occur. The platelets become granular, the leucocytes undergo fatty degeneration and necrosis and break down, and the red cells become decolourised and fragmented, and the thrombus is converted into a fibrinous plug, cord, or mass. By an extension of these changes the thrombus may become softened and loosened, and fragments may be detached, forming emboli. If infection occur, the process of softening may be more intense, leucocytes invade the thrombus, and it becomes a semi-purulent mass, easily broken down and detached, and the fragments form septic emboli. In the veins calcification is not infrequent, a phlebolith being formed.

In other cases the thrombus becomes more or less organised. It may be invaded by leucocytes and gradually absorbed; new cells are derived from the endothelium and the fixed cells of the part; new vessels spring from the vasa vasorum, and the young tissue, at first rich in cells, becomes fibrous and contracts, or the vessels may extend and a cavernous tissue fill the lumen of the thrombosed vessel, and by the disappearance of the septa even result in the restoration, more or less complete, of the lumen of the vessel, save for a few fibrous threads or bands.

CAUSES OF THROMBOSIS.—Various factors generally contribute to induce thrombosis. These are (1) slowing of the blood-stream. This by itself is not sufficient, but is an important predisposing factor and frequently determines the location of the thrombus. Ligation of vessels leads to thrombosis up to the nearest collateral branch. The ligature causes stagnation of blood and also usually rupture of the intima; the latter is a necessary event for the proper occlusion of a vessel by ligature. (2) Alteration in the vascular walls. This is one of the most important factors, and occurs from wounds, inflammation, compression, etc. In this, too, great variation is seen; an aseptic lesion has slight tendency to cause thrombosis, but if infection occur considerable thrombosis may ensue. The aorta may be extensively diseased, with little or no thrombosis.

(3) Foreign bodies may give rise to thrombosis—*e. g.* derived from without, as fish-bones, pins, etc., or from within, as parasites, blood-clot, particles of a tumour, etc. (4) Increase in the coagulability of the blood. This may play a part, and Wright has shown that thrombosis in typhoid fever may be preceded by an increase in the coagulability of the blood. The so-called "marantic thrombi," which are not infrequent in diseases attended with cachexia and prostration, such as fevers, anæmia, etc., are perhaps partly due to this cause, enfeebled heart's action and slowing of the circulation, with the resulting malnutrition of the endothelium, being conducive. Many of the marantic thrombi are, however, probably infective. In typhoid fever there is also a sub-endothelial infiltration which may undergo necrosis together with the overlying endothelium, and form the starting-point of the thrombosis.

Various substances have the property of inducing intra-vascular clotting, the principal of which are peptone, proteoses, snake-venom, and extracts of cells. These substances probably act by increasing the amount of fibrin ferment. Many bacterial toxins seem to contain substances allied to the proteoses, and this might explain the frequency of thrombosis in infective processes. But the amount of proteose required to produce intravascular clotting is far larger than the amount of proteose ever found in a bacterial infection. Wright ascribes an important influence to increase in the calcium salts, derived particularly from the milk which forms so large a part of the diet of fever patients, especially in typhoid. He finds[1] that during convalescence, the period at which thrombosis generally occurs in typhoid, the coagulability of the blood is often four and a half times greater than in the acute stage, and the lime-salts about twice the amount present in normal blood. Based on this theory, he suggests that when the risk of intestinal hæmorrhage has passed citrate of soda may be given and the milk be treated with this salt in order to "decalcify" and diminish the excess of lime-salts.

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[1] *Brit. Med. Journ.*, 1902, vol. ii, p. 1708.

In the puerperium no increase in the coagulability of the blood could be detected by Douglas.[1]

In many infective diseases there seems to be an increase in the number of blood-platelets, a point of interest considering the important part these structures appear to play in thrombosis.

Attention has also been directed by Flexner[2] and others to the *rôle* of agglutination in the production of thrombosis. In many infective diseases—*e. g.* pneumonia[3] and typhoid—the chromocytes are prone to marked rouleaux formation and agglutinate into large masses. This agglutination is due to the development of agglutinating substances or agglutinins for the red corpuscles, and such substances are present in cultures of many species of micro-organisms. The primary event in the formation of many marantic thrombi may therefore be agglutination of the chromocytes, and chromocyte clumps have actually been detected in typhoid fever and pneumonia. The capillary hyaline thrombi are probably of this nature. The coagula which appear in the heart in many forms of experimental poisoning—*e. g.* by ricin—are not true clots, at least at first, but masses of agglutinated corpuscles.

OCCURRENCE OF THROMBOSIS IN DISEASE.—Thrombi are met with most commonly in the heart and veins, less so in the arteries. *In the heart* thrombosis may occur in any condition associated with slowing of the blood-current—*e. g.* valvular disease, dilatation, pulmonary disease, arteriosclerosis, and renal disease—but is uncommon in infective diseases. The young vegetations of endocarditis are actually genuine mural thrombi, though not usually described as such. Polypoid thrombi are sometimes met with, and rarely free or ball-thrombi, due to the deposition of fresh material on a small mass separated from the endocardium. Cardiac thrombi are most frequent in the auricular appendices and the ventricular apices, these being the sites of most pronounced blood-stagnation.

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[1] *Brit. Med. Journ.*, 1904, vol. i, p. 709.

[2] See *Amer. Journ. of the Med. Sciences*, August, 1903.

[3] See Shattock, *Path. Soc. Trans.*, vol. l, 1899, p. 279.

Very frequently moist, pale, yellowish, non-adherent clots are met with in the heart post mortem. These must be distinguished from true thrombi, which are drier, firmer, greyish, and more granular and friable. These clots are often stated to be formed during the death agony, but the majority are probably simply post-mortem clots, their pale colour being analogous to the buffy coat of clots in shed blood.

Thrombosis in the veins is the commonest of all forms of thrombosis. It is much more frequent in the lower than in the upper extremity, in the proportion of 50 to 1. It generally occurs in the course of infective diseases—typhoid, septicæmia, influenza—and after parturition (*phlegmasia alba dolens,* due to septic infection), also in chlorosis, tuberculosis, and cachectic states. The femoral vein is the usual site of the thrombosis. In connexion with septic processes the thrombosis takes place in neighbouring veins—*e. g.* in the cerebral sinuses in mastoid disease, in the portal vein in pylephlebitis, in the mesenteric veins in intestinal ulceration, etc.

Arterial thrombosis may occur round an embolus, but is most commonly associated with disease of the arterial walls, *e. g.* arteriosclerosis, aneurysm, and particularly syphilitic endarteritis. The cerebral and cardiac arteries are those chiefly involved. Pulmonary thrombosis occurs after parturition and has been ascribed by Playfair to a primary thrombosis, but is probably generally secondary to embolism.

RESULTS OF THROMBOSIS.—These vary with the site and extent of the process. In "terminal vessels" (see p. 264) necrosis must ensue, and in the extremities if large vessels be thrombosed, and, particularly if the collateral circulation is interfered with through disease of the vessel walls, gangrene may follow. A certain amount of œdema is common—*e. g.* after thrombosis of the femoral vein. From softening and fragmentation of the thrombus embolism may ensue. Extensive pulmonary or cardiac thrombosis is necessarily incompatible with life.

EMBOLISM.[1]

Embolism is the impaction in some part of the vascular system of any undissolved material brought there by the blood-current (Welch). The material so transported is termed an embolus.

The embolus may consist of—

(1) The whole or fragments of a thrombus.

(2) Tumour fragments derived from a tumour invading a blood-vessel.

(3) Cellular fragments derived from the liver, in rupture, degeneration, or hæmorrhage, from the placenta, giant cells from the bone-marrow in leukæmia, etc.

(4) Fat-drops, particularly in fracture with injury of the bone-marrow, and in contusion of the subcutaneous adipose tissue.

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[1] On Embolism, see an exhaustive article by Welch in Clifford Allbutt's *System of Medicine*, vol. vi, p. 228.

(5) Animal and vegetable parasites.

(6) Foreign bodies (rare) and air. If a vein be injured and air gain access, embolism may result. Air-embolism is especially to be dreaded if any of the large veins near the thorax be opened, since the air may be directly aspirated by the negative pressure during inspiration.

Emboli as a rule follow the direction of the blood-current and become arrested as soon as the lumen of the vessels becomes too small to allow of their passage, or occasionally at an arterial bifurcation. Emboli originating in the large veins, right heart, or pulmonary artery become impacted in the branches of the pulmonary artery; those arrested in the systemic arteries come from the pulmonary veins, left heart, aorta, or some artery between the heart and the embolus; and emboli arising in the radicles of the portal vein lodge in the hepatic branches of the vein in the liver. Exceptionally, if there be a defect of the interauricular or interventricular septum in the heart—*e. g.* a patent foramen ovale—emboli from the systemic veins may pass directly from the right to the left heart and become arrested in the systemic arteries instead of the pulmonary arteries; this is known as *"paradoxical"* or *"crossed" embolism.* The same may occur through a patent ductus arteriosus.

Retrograde embolism takes place when the embolus is transported in a direction opposite to that of the normal blood-flow. This is a rare event and seems to occur only in the veins. It is usually explained by a temporary reflux in the venous current, aided perhaps by imperfect valves. Ribbert, however, suggests that when there is complete, or almost complete, venous stasis, pulse-waves occur which gradually force the embolus backwards. In this way an embolus in the ascending vena cava may be carried into the renal or hepatic vein. Tumour fragments may similarly be carried backwards, and this fact accounts for the anomalous distribution of metastatic growths in cases of malignant disease—*e. g.* secondary deposits in the longitudinal sinus in mammary carcinoma (Arnold). Liver-cells have been met with in the cerebral and renal veins in cases of hepatic necrosis (Welch).

Emboli may also be carried by the blood-stream reversed from its normal direction in consequence of obstruction of veins by compression, etc. A reversal of the current is not infrequent in lymphatic vessels and plays an important part in tumour metastasis.

It is possible for tumour-cells, provided they are not of large size, to pass through the pulmonary capillaries and thus originate metastases apparently of anomalous distribution. The pulmonary capillaries are so large that they may permit the passage of emboli which would be arrested in the smaller systemic capillaries.

CHARACTERS OF EMBOLI.—Emboli derived from ordinary fibrinous coagula or thrombi have much the same characters and structure as the latter. They may be approximately spherical and then, as a rule, completely fill the lumen of the vessel in which they have lodged, or they may be elongated and cylindrical, or irregular in shape, and usually lodge on an arterial bifurcation. The embolus is generally the starting-point of secondary thrombosis which plugs the vessel on both sides of it up to the nearest branches. A recent embolus is distinguished from a thrombus by lying loosely in, or being but slightly attached to the walls of, the vessels, but it may be difficult or impossible to distinguish an old embolus from a thrombus, since secondary changes occur in it similar to those already described for a thrombus.

Emboli, like thrombi, may be aseptic or "bland," or infective or "septic," if infected with micro-organisms. Septic emboli are the cause of the secondary abscesses in pyæmia.

Fat embolism probably occurs to a slight extent in every case of fracture of a bone with fatty marrow. Occasionally it may be so extensive as to cause death, in which case fat globules will be found in large numbers in the smaller pulmonary arteries and capillaries, and even in those of other organs. Injury or disease of any fatty organ or tissue may be followed by fat embolism. If recovery ensues, the fat is got rid of partly by saponification by a lipase in the blood, partly through phagocytic activity.

Air-embolism is almost always due to the entrance of air into the circulation as the result of the severing of a large vein, occasionally by the entrance of air from the uterus, or of gas from the stomach or intestine. Small amounts of air rapidly introduced are speedily fatal in man, who seems particularly susceptible, for animals can bear the introduction of comparatively large quantities without harm. After death from air-embolism the branches of the pulmonary arteries are found filled with bubbles, and the right heart distended with frothy blood; it is rare for the air to pass through the pulmonary capillaries into the systemic circulation. Various explanations have been given of the cause of death in air-embolism. One suggests that the frothy mass of blood, being compressible from admixture with air, cannot be properly propelled by the right ventricle; the left ventricle therefore receives little blood, the aortic pressure falls, and death ensues. Another theory is that the frothy blood cannot be propelled through the pulmonary and coronary capillaries; probably all these factors contribute to the fatal event.

The mere presence of gas-bubbles in the heart and vessels is no proof that air-embolism has occurred unless found shortly after death or the entrance of air has actually been observed. For post-mortem decomposition, and particularly infection with an organism, the *Bacillus aerogenes capsulatus* of Welch and Nuttall, lead to a rapid and abundant development of gas after death. Caisson disease and diver's palsy have been attributed to air-embolism. Men working under water in compressed air in air-locks (caissons) and divers occasionally suffer on exit from the compressed air (not while in it) from numbness, dizziness, vomiting, chills, muscular and joint pains, failure of pulse, etc., or in more serious cases from paralysis, diplopia, deafness, and coma which may end in death. The workmen themselves have found by experience that their symptoms disappear on again entering the compressed air—*i.e.* by recompression. Hill and Macleod[1] have recently studied the disease and find that the symptoms must be ascribed to too rapid decompression. During compression the circulation is unaffected, but the gases in the blood increase in amount, according to Dalton's law, and ultimately the blood may be completely saturated. On decompression a rapid escape of gas-bubbles in the blood-vessels and tissue fluids takes place. An animal exposed for four hours to a pressure of 8 atmospheres and quickly decompressed "is like an opened bottle of soda-water; the fluids of the body generally effervesce." Recompression causes the bubbles to go into solution again. The bubbles after rapid decompression can be seen post mortem "in the blood-vessels, in the heart, retinæ, aqueous humour, connective-tissue spaces, etc. The alimentary canal is blown out with gas. The bubbles produce cyst-like cavities in the solid organs—*e.g.* in the central nervous system and the liver. The cells are compressed round these cysts. The varying symptoms of caisson sickness are due to the varying seat of the air-emboli." The researches of Hill and Macleod prove, therefore, that caisson disease is due to air-embolism. The prevention of the disease is simple, viz. *gradual* decompression.

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[1] *Journ. of Hygiene*, vol. iii, 1903, No. 3, p. 401.

Parasitic emboli are not frequent. They may consist of plugs of bacteria, protozoa, the embryos of filariæ, and other blood parasites.

Effects of embolism.—The effects of embolism are twofold—mechanical, depending on the point of lodgment, and specific, depending on the nature of the embolism, whether bland or infected, and whether composed of dead cells or of cells capable of further proliferation. Closure of a large artery—*e. g.* the pulmonary, coronary, or bulbar—may cause sudden death. In other situations necrosis or gangrene may ensue, and interference with function, temporary or permanent—*e. g.* in the nervous system hemiplegia or other paralysis (if in the pons hyperthermia may occur), in the retina blindness, etc.—the exact result depending on the situation of the lesion. In the extremities after a time the collateral circulation is usually established, and recovery is complete (see p. 247). If, however, there be cardiac weakness or vascular disease, gangrene may ensue. If the emboli be septic secondary and perhaps multiple abscesses—*i. e.* pyæmia—may result, or embolic aneurysms. The latter seem to be due to acute softening of the arterial wall from the action of the infective agent and subsequent dilatation. Emboli of tumour fragments may cause secondary or metastatic growths, as already mentioned.

An *infarction* results from the occlusion, usually by embolism and secondary thrombosis, of a "terminal" or "end" artery. By this is meant an artery supplying a region, and having no anastomosis with neighbouring vessels (except, of course, through capillaries). Such arteries are found in the spleen, kidney, brain, retina, and myocardium. In the brain it is the deeper arteries, not those of the pia, etc., which are terminal in character. The superior mesenteric and the pulmonary arteries also possess very imperfect collateral anastomoses. The blocking of a terminal artery is quickly followed by anæmia of the part supplied by it, and sooner or later by coagulative necrosis, and death of this area, which is then known as an *infarct.* Owing to the dichotomous branching of the artery the infarct is pyramidal in shape, the base being at the surface of the organ, the apex at the point of occlusion. If the death of the part follows soon after the occlusion, the area remains pale and bloodless, the *non-hæmorrhagic* or *white infarct,* a zone of hyperæmia generally surrounding it; but in some cases the area becomes engorged with blood, which has been ascribed to regurgitation from the capillaries, and perhaps also from the veins, the part becomes infiltrated with fluid and with blood-corpuscles which have escaped from the vessels by diapedesis, and this condition is designated a *hæmorrhagic infarct.* Cohnheim ascribed the hyperæmia in hæmorrhagic infarct to regurgitation from the veins, but a number of experiments negative this view. Tying the veins in an area in which occlusion of an artery is followed by a hæmorrhagic infarct *increases* the hyperæmia and hæmorrhage, and renders an infarct hæmorrhagic which otherwise might be anæmic. The blood which accumulates in the infarct is derived, therefore, from the capillaries and arterial anastomoses, if these exist. A hæmorrhagic infarct may subsequently become decolourised and pale. Non-hæmorrhagic infarcts are most typically seen in the spleen and kidney, the pyramidal area is yellowish-white and contracted, forming a puckered scar, and, microscopically, the cells, which have undergone coagulative necrosis, are wholly or partially necrotic, and stain badly or not at all. The hæmorrhagic infarct is often well seen in the lung; being engorged with blood, it forms a swollen patch of a deep plum colour, like damson cheese.[1] In the brain occlusion of the vessels is usually followed, not only by necrosis, but by softening and liquefaction of the necrotic area.

Although the branches of the hepatic artery and portal vein are anatomically terminal vessels, the capillary anastomosis is so free that infarction is a rare result of their occlusion. A few cases have been recorded, however, in which after embolism or thrombosis of certain branches a condition resembling hæmorrhagic infarction has ensued.

An old infarct, if small, may be almost entirely absorbed; if larger, is replaced by fibrous tissue, or, in the brain, sometimes by cyst-formation. Calcification may also occur.

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[1] Hamilton ascribes these hæmorrhagic areas in the lung to actual hæmorrhage or apoplexy, but the evidence is in favour of their being infarcts due to embolism and thrombosis (Welch).

CHAPTER XIII.

DISEASES OF THE HEART AND VESSELS.

Certain general conditions and diseases of the heart may first be described, after which the diseases of the various constituents of the heart and of the vessels will be discussed.

VARIATIONS IN THE CARDIAC RHYTHM.

Tachycardia, or palpitation, is an increase in the frequency of the heart-beat. It is often present in dyspepsia, and is a marked feature of exophthalmic goitre. It is probably usually caused by inhibition of the tonic action of the cardio-inhibitory centre. In influenza, diphtheria, and other infective diseases, tachycardia is common, and is due to a toxic action on the local nerve-centres in the heart.

Bradycardia, diminution in the frequency of the heart-beat, is rarer than tachycardia. It is met with in jaundice (owing to the action of the bile-salts), meningitis, and cerebral tumour, and may be due to the action of certain poisons—*e. g.* digitalis. It is probably due to stimulation of the vagus.

Intermittence is often present in valvular disease, and may be caused by poisons—*e. g.* tobacco. In some cases it is due to weak and strong ventricular contractions alternating; in others the cause is unknown.

Irregularity is also frequent in cardiac disease, but its cause is uncertain. A condition of hemisystole, a contraction of one ventricle without the other, may perhaps occur and be the explanation of some forms of irregularity and intermittency.

HYPERTROPHY AND DILATATION OF THE HEART.

These two conditions are so frequently associated that they may conveniently be discussed together. Hypertrophy is applied to the increase of the muscle-substance, dilatation to the enlargement of the cavities, with or without hypertrophy of the muscle, and either condition may be total or partial. Any condition which causes an increase in the amount of work performed by the heart leads to hypertrophy—*e. g.* adherent pericardium if not too extensive, valvular disease, and physical exertion. Even long-continued palpitation or tachycardia, such as results from toxic agents—*e. g.* tobacco, or in exophthalmic goitre—may act similarly. Nephritis and Bright's disease are also followed by cardiac hypertrophy, but the mechanism of its production is obscure, and will be discussed later. General arteriosclerosis is another cause, and acts by impeding the circulation through the arterioles. Valvular disease of the aortic orifice is especially the cause of hypertrophy of the left ventricle; in insufficiency more blood has to be propelled through the vascular system owing to the regurgitation, in stenosis there is more difficulty in emptying the left ventricle. Stenosis of the aorta (congenital or acquired) has a similar effect.

Lesions affecting the mitral orifice first act on the left auricle, causing dilatation with moderate hypertrophy, and the resistance may subsequently be transmitted to the right side of the heart through the pulmonary system, and produce some hypertrophy of the right ventricle. Emphysema and pulmonary fibrosis, by obstructing the pulmonary circulation, also cause hypertrophy of the right heart. Lesions of the pulmonary or tricuspid orifices are rare, but, if present, bring about the same condition of the right heart.

In all cases probably the first effect is to induce dilatation, which is subsequently compensated for by hypertrophy. In the later stages of cardiac disease dilatation again ensues, principally on account of degeneration of the hypertrophied muscle. As regards the auricles, hypertrophy is always accompanied by some dilatation.

CERTAIN GENERAL DISEASES OF THE HEART.

Angina pectoris is a condition characterised by intense precordial pain, frequently radiating down the left arm, accompanied by dyspnœa and cardiac distress, and, sooner or later, ending fatally. It is very frequently associated with atheroma of the coronary arteries and degeneration of the cardiac muscle. Cohnheim observed that after ligature of a large branch of a coronary artery the rhythm of the heart becomes irregular, and then the heart suddenly stops beating in a condition of diastole. Probably what occurs in angina is a sudden dilatation of the heart due to cardiac insufficiency, the result of malnutrition, the pain being caused by pressure on the cardiac nerves.

With regard to the distribution of pain down the arm which is so frequent in angina pectoris, Graham Steel[1] suggests the following explanation: Impressions arising in the heart, having arrived at the associated

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[1] *Med. Chronicle*, 1905, March and April.

segment of the cord, proceed to the grey matter of the cerebrum, and the impressions or pain are referred by it to the parts corresponding with the afferent supply of the grey matter into which diffusion has taken place. According to Head, the ascending aorta refers its pains to the somatic distribution of the third and fourth cervical nerves with that of the first, second, and third dorsal nerves, while the ventricle and auricle are associated with the dorsal spinal segments from the second to the eighth. The area of the somatic distribution of the first and second dorsal spinal segments is the inner side of the arm and forearm; hence the pain is felt in this region.

STOKES-ADAMS' DISEASE.—This disease, first described by Adams (of Dublin) in 1827, is, according to Osler,[1] characterised by (1) a profound disturbance in the automatic mechanism of the heart: true bradycardia, hemisystole (false bradycardia), and allorythmia; (2) nervous symptoms: vertigo, syncope, pseudo-apoplexy, and epileptiform attacks; (3) secondary symptoms: Cheyne-Stokes' breathing, cardiac asthma, angina pectoris, and the vasomotor accompaniment of profound heart-shock. The post-mortem changes are not constant. In a few cases coarse lesions of the nervous system have been found, in a small number no lesions whatever, in a large proportion of the cases arteriosclerosis is present.

The pathology of this disease is obscure, but it is not unlikely that it is a condition of "heart-block" or independent auricular systole without corresponding ventricular contractions, the vertigo, pseudo-apoplexy, etc., being due to resulting cerebral anæmia. It has been noted that in some of the cases jugular pulsations may occur of greater frequency than the ventricular contractions and ascribable to corresponding auricular contractions. It would appear that while the auricles respond normally to the various influences which come to them, the ventricles are not so influenced. Erlanger,[1] by clamping the auriculo-ventricular bundle in which lies the only muscular connection between auricles and ventricles in the dog, produced a condition of heart-block in which the contractions of the auricles were to those of the ventricles in the ratio of 2 : 1 or 3 : 1. He therefore concludes that the seat of the lesion will probably be found in this region.

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[1] *Lancet*, August 22nd, 1903.

DISEASES OF THE PERICARDIUM, MYOCARDIUM, AND ENDOCARDIUM, AND THEIR EFFECT ON THE CIRCULATION.

Diseases of the Pericardium.

INFLAMMATION OF THE PERICARDIUM, pericarditis, is most frequently met with in acute rheumatism. It also occurs in scarlatina and renal disease, as an extension from the inflamed lung in acute pneumonia, or from pleuritic or mediastinal inflammation, from deposits of tubercle or of malignant disease, and rarely from traumatism. It is generally of a fibrinous or sero-fibrinous nature, and is usually independent, but may be associated with myocarditis or endocarditis. The serous membrane loses its shining appearance and becomes dull and velvety, more or less injected, and minute extravasations may be present, and the deposit of fibrin may form a delicate membrane on the inflamed patches. The serous exudation is usually inconsiderable, a few c.c.'s, *dry pericarditis*, but may be more or less abundant, from many c.c.'s to ½–1 litre, the fluid being generally yellowish, clear, and transparent, but sometimes turbid from abundance of corpuscles and fibrin. In certain instances, particularly in malignant disease and blood-poisoning, it may be bloody (*hæmorrhagic pericarditis*). The endothelium of the serous membrane is more or less desquamated, the sub-endothelial connective tissue infiltrated with leucocytes, and the vessels engorged, and the patches are covered with laminated fibrin which may subsequently organise, forming "milk spots," or binding the two surfaces of the membrane together (*adherent pericardium*).

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[1] *Johns Hopkins Hosp. Bull.*, No. 171, June, 1905, p. 234.

"Milk spots" are sometimes met with in cases of enlarged heart without any history of an antecedent pericarditis, and have been ascribed to a chronic inflammation set up by increased friction.

The chief seat of local pericarditis is the base, about the origin of the great vessels, but the condition may be more or less general or diffuse.

Effects of pericarditis.—Acute pericarditis is accompanied by more or less precordial pain, due to stimulation of nerve-fibres beneath the inflamed patches, and rapid and weak action of the heart, partly due to involvement of the heart-muscle and partly to a lessening of the normal inhibitory influence of the vagus. The rubbing of the two surfaces of roughened membrane together generates the "to and fro" friction rub, usually best heard just to the left of the sternum, which may, however, not be heard or may disappear if accumulation of fluid separates the two surfaces. The latter event may seriously interfere with the circulation and the heart's action if of any extent, a rapid accumulation being more serious than a slow one. The fluid causes a rise in the intra-pericardial pressure and may be imitated experimentally by injecting oil into the pericardial sac of an animal. The effect of such an injection is a fall of blood-pressure in the systemic and pulmonary arteries, with a rise of venous pressure, and if the injection be continued these differences become so marked that the circulation of the blood finally ceases, the arterial pressure falling to zero. The reason for this is that normally the inflow of blood into the right auricle is largely determined by the difference of pressure which exists outside and inside the thorax; by the accumulation of fluid this difference becomes less and less, the blood tends to accumulate in the large veins, and the right auricle receiving less and less blood, less and less blood is transmitted to the left heart, with therefore a corresponding fall in aortic pressure. Orthopnœa and cyanosis become marked in extreme cases, the latter being dependent on venous engorgement (the veins may be distended and the external jugular pulsating) and imperfect blood-aeration. The area of cardiac dulness becomes increased, but the normal shape of the pericardial sac is retained—*i. e.* pyramidal with the base downwards.

Adherent pericardium interferes with the due working of the heart, which, therefore, hypertrophies to overcome the resistance, unless the adhesions be very extensive, in which case, as the resistance cannot be overcome, atrophy may ensue. Moreover, if the heart-muscle cannot contract in a normal manner, the normal action of the valves may be interfered with, and valvular incompetence occurs.

Hydropericardium, dropsy of the pericardial sac, is generally a part of the general dropsy of chronic renal or cardiac disease, but occasionally may result from pressure on the pericardial veins by mediastinal tumours or aortic aneurysm, from chronic pulmonary disease, or affections associated with grave cachexia. The amount of fluid varies from 200–300 c.c. to a litre or more (a small quantity of fluid, 10–30 c.c., occasionally 100 c.c., is as a rule found in the pericardial sac irrespective of the cause of death). The fluid is usually clear and yellowish, but rarely may be milky from admixture with chyle (*chylopericardium*), blood-stained, or yellow if there be jaundice. The endothelial cells become macerated, swollen, and partially shed in long-standing cases.

Hæmopericardium, blood in the pericardial sac, may arise from traumatism, rupture of the heart or of an aneurysm, in the course of certain blood conditions, *e. g.* scurvy and purpura, and from deposits in the membrane, especially cancer. Occasionally pericarditis is associated with some hæmorrhage.

Pyopericardium, pus in the pericardial sac, may be secondary to a simple pericarditis, but is usually a pyæmic infection, or is traumatic, or is an extension from a neighbouring part. An abscess, or empyema, may rupture into the pericardium. The organisms found in the pus are generally the various pyogenic cocci, streptococci, the pneumococcus, or the tubercle bacillus.

Pneumopericardium, gas in the pericardial sac, is very rare, and pus is generally present as well (*pyopneumopericardium*). It may arise from a penetrating wound of the chest or fractured rib, now and then from decomposition.

Tuberculosis rarely affects the pericardium. It may be primary and a part of a general infection, but is usually secondary to tuberculosis of the lungs or mediastinal glands. Few or many discrete tubercles may be present and may be attended with fibrinous exudation, which may subsequently become organised with the formation of adhesions. *Actinomycosis* has also been recorded. *Syphilis* does not seem to affect the pericardium, unless, perhaps, certain indurative changes that have been described are due to it.

Carcinoma and *sarcoma* are rare, but when present are usually secondary, or develop by continuity. *Lipoma* and *fibroma* have been described, also *hydatids* and *cysticerci*.

Diseases of the Myocardium.

HYPOPLASIA AND ATROPHY. — Hypoplasia, defective development, of the heart, is occasionally met with without obvious cause, and of the heart and vessels is sometimes associated with chlorosis.

Atrophy of the heart is seen in wasting diseases, malignant disease, phthisis, and diabetes, and then involves the whole organ, and adherent pericardium, if extensive, may lead to the same result. Partial atrophy of the left ventricle may occur in consequence of mitral stenosis, or of stenosis of the coronary arteries, causing deficient blood-supply. The heart is diminished in size and weight, the muscle is often flabby, thinned, and pale, or it may be brownish from deposition of pigment (*brown atrophy*). The muscle-fibres may be atrophied and degenerate, with an increase of the interstitial fibrous tissue.

MYOCARDITIS.—Acute myocarditis, or inflammation of the cardiac muscle, is often associated with pericarditis and endocarditis, but is then usually limited in extent. Extensive myocarditis may be associated with infective diseases, especially diphtheria, scarlatina, enteric, and rheumatism. The capillaries dilate, the interstitial tissue becomes infiltrated with round cells, and the muscle-fibres show more or less cloudy swelling or fatty degeneration. Resolution may be complete but more frequently some fibrosis remains. The septum and the left ventricle are the parts most affected.

Acute suppurative myocarditis, with the presence of miliary or even larger abscesses, may occur in the course of general pyæmia, or rarely by extension from a purulent pericarditis or an infective endocarditis.

Chronic interstitial myocarditis is a condition in which there is an extensive diffuse fibrosis. It may follow from an acute myocarditis, but is generally associated with cardiac endarteritis and arteriosclerosis. As a sequel, bands of fibrous tissue may form, which may be visible as greyish streaks in the cardiac muscle, particularly in the septum, anterior wall of the left ventricle, and tips of the papillary muscles.

FATTY INFILTRATION AND DEGENERATION are the commonest and most important lesions of the myocardium.

Fatty infiltration is an accumulation of fat on the surface of the heart and between its muscle-fibres. A certain amount of fat is normally present under the visceral pericardium, particularly in the grooves between the auricles and ventricles, and this becomes increased and in addition fat becomes deposited in the substance of the heart-muscle between the fibres. It is most frequently seen as a part of general obesity.

Fatty degeneration is especially liable to occur in hypertrophy from any cause, and also in certain toxæmic states, phosphorus and arsenic poisoning, and in diphtheria and other infective diseases. Hypertrophied muscle is very prone after a time to undergo fatty degeneration, and fatty degeneration of the heart-muscle is one of the principal causes of sudden death. The change may be general or may be limited to the left ventricle. The heart-muscle loses its red colour and becomes pale, or in marked cases yellowish; it may feel greasy, and on scraping a greasy semi-fluid may be collected. Microscopically, fine droplets of fat are found deposited in the substance of the muscle-fibres, which in advanced cases may lose their striation and their nuclei. Cloudy swelling may precede, and more or less deposition of pigment and fibrosis may accompany, the condition.

CLOUDY SWELLING frequently affects the cardiac muscle in acute infective diseases and causes swelling of the fibres, loss of striation, with deposition of fine granules and degeneration and disappearance of the nuclei. Fatty changes may succeed the cloudy swelling.

LARDACEOUS INFILTRATION may occur in the heart in conditions associated with lardaceous infiltration elsewhere. It affects the smaller blood-vessels and interstitial tissue.

SEGMENTATION AND FRAGMENTATION of the heart-muscle occurs in many infective processes and in death from suffocation, the papillary muscles of the left ventricle being most affected. It seems to be brought about by a disproportion between the vigour and order of the muscular contraction (Hektoen).

EMBOLISM AND THROMBOSIS of the coronary arteries and their branches are of considerable importance. Being terminal arteries, occlusion of a branch of any size is followed by serious nutritive disturbance and degeneration. Embolism is relatively infrequent, originates from particles of fibrin or atheromatous material derived from acute or chronic endocarditis, and is most frequent in the anterior branch of the left coronary. Thrombosis is more common and occurs particularly in the course of atheroma. Sudden occlusion of a large branch may cause sudden death. The occlusion of smaller branches is followed by anæmic necrosis and is most frequent at the apex of the left ventricle. Fatty degeneration and disintegration of the muscles ensues and may lead to rupture or aneurysmal dilatation.

Aneurysm of the coronary arteries occasionally occurs, may be single or multiple, the dilatations varying from a pea to a cherry in size, and generally terminates in rupture.

Aneurysm of the heart, a local pouching of its walls as opposed to a general dilatation of its cavities, is a rare affection and generally results from coronary obstruction with subsequent degeneration or gummatous infiltration occasionally from wounds, fatty degeneration, etc. The left ventricle is the most frequent site.

Rupture of the heart is a rare event and is always due to pre-existing disease, aneurysm, gumma, or neoplasms, and occurs after strain of some kind. *Tuberculosis, neoplasms,* and *parasites* are very rare. *Syphilis* in the form of a fibroid infiltration is perhaps not infrequent, but gumma is rare.

Diseases of the Endocardium.

Endocarditis.—Inflammation of the endocardium may be acute, infective, or chronic, but there is no hard and fast line between these, one form often passing into another.

Acute endocarditis is most frequent by far in the course of acute rheumatism. It also occurs in scarlatina and other infective diseases, septicæmia and pyæmia, pneumonia, gonorrhœa, etc. The disease attacks the valves much more frequently than other parts, the left heart more frequently than the right, and the mitral more frequently than the aortic valve. It is not the extreme edge of the valves which is most affected, but the line of contact—*i. e.* 2 mm. from the free margin. The process commences with dilatation of the sub-endothelial vessels, exudation of leucocytes and fluid into the sub-endothelial connective tissue, swelling, and desquamation of the endothelium, and deposit of fibrin on the surface enclosing chromocytes and leucocytes. The fibrin acts as a foreign body and more and more fibrin may be deposited, so that a warty excrescence is the result, the vegetation. As the process subsides, if slight the fibrin may be nearly entirely removed and healing result, but usually this is not possible, the fibrin becomes infiltrated with round cells and ultimately spindle cells and fibrous tissue develop, and a fibrous nodule is formed. The changes bringing this about are comprised under the term "chronic endocarditis." The vegetations are usually multiple and lie side by side in close contact, so that a more or less irregular ridge of fibrous tissue is ultimately produced. By the adhesion of the fibrinous surfaces and contraction of the cicatrices various puckerings of the valves result which prevent their proper closing, or a "button-hole" valve is produced. These changes may obstruct the flow of blood (stenosis), or may allow the blood to flow back (regurgitation or insufficiency). Mitral regurgitation is by far the commonest form of valvular disease.

In some cases, owing to infection of the lesion, instead of the fibrin becoming fibrous and healing ensuing, necrosis and solution occur and excavations form which are practically ulcers; this is *ulcerative* or *infective endocarditis,* and a general septicæmia or pyæmia often results. The micro-organisms most commonly met with are, in order of frequency, the streptococcus, *Diplococcus pneumoniæ, M. pyogenes aureus,* and occasionally others —*e. g.* the colon bacillus, gonococcus, influenza bacillus, etc. Some amount of myocarditis probably always accompanies endocarditis, and pericarditis is frequent.

EFFECT OF VALVULAR LESIONS ON THE CARDIAC SOUNDS.—The first sound of the heart is caused partly by the closure of the auriculo-ventricular valves, partly by the contraction of the heart-muscle. The second sound is caused by the sudden closure and stretching of the aortic valves. Should the two sides of the heart not synchronise, "reduplication" may result. An abnormal sound accompanying or replacing a normal cardiac sound is termed a *murmur*. If there be *obstruction* at the aortic orifice, a modification will be produced at the time when the blood is flowing from the ventricle into the aorta—*i. e.* at the period of the ventricular systole or during the first sound. Therefore aortic obstruction causes a replacement of the first sound, usually by a harsh or rough, occasionally musical, systolic murmur. Pulmonary obstruction similarly causes a systolic murmur. If there be *regurgitation* at the aortic orifice, a modification of the second sound will ensue at the time when the aortic valves should be closing, and afterwards during a portion of the diastole—*i. e.* the murmur will be diastolic.

If there be *obstruction* at the mitral orifice, a murmur will be heard during the flow of blood from auricle to ventricle—*i. e.* it will precede the first sound, or be presystolic. If there be *regurgitation* at the mitral orifice, the murmur will be heard during the ventricular systole—*i. e.* it will be systolic in time. In tricuspid regurgitation a systolic murmur will similarly be heard.

Formerly it was believed that the murmur was produced by the passage of the blood over a rough surface, but that this is not the whole explanation is proved by the fact that murmurs may be heard (*e. g.* in anæmia) when the endocardium and valves are perfectly healthy. At present the production of murmurs is regarded as being caused by eddies and churning of the blood as it flows from a narrower into a wider channel. As regards the anæmic murmurs, these may be explained by the stretching of the heart and vessels and alteration of tension and capacity so induced due to the increase in the volume of the blood in this condition (see p. 228).

The conduction of cardiac murmurs has not been completely explained. Thus a mitral obstructive presystolic murmur is generally very localised, whereas a mitral regurgitant systolic murmur may be heard widely and particularly towards the axilla, explicable on the fact that the heart's apex at the systole is in close contact with the wall of the thorax. Similarly, while the aortic obstructive systolic murmur is generally heard best at the second right costal cartilage, the aortic regurgitant diastolic murmur is frequently audible only at the ensiform cartilage.

EFFECTS OF VALVULAR LESIONS ON THE HEART.—Whether the blood is obstructed in its passage from the heart or regurgitates back into one of the cavities, the first effect is to produce more or less dilatation, since in either case there is an increase in the amount of blood contained in the ventricle or auricle at the height of the systole. An increase in the amount of blood contained in the heart at a given time produces, however, a far greater effect on the size of the ventricle than on that of the auricle, because the latter may be considered as a part of the relatively large pulmonary venous system, which is unprovided with valves, while the cavity of the ventricle is bounded by the auriculo-ventricular and semilunar valves. Dilatation of the auricle is therefore usually slight in amount, while that of the ventricle may reach considerable dimensions.

Dilatation is usually succeeded by a compensatory hypertrophy of the cardiac muscle, to overcome the increased resistance to which this is subjected in endeavouring to maintain the normal circulation. The hypertrophy will be greatest in those parts subjected to most strain, and, within limits, under those conditions which produce the most resistance to the circulation. Hypertrophy reaches its maximum in the left ventricle in cases of aortic disease.

Should dilatation proceed beyond certain limits, cardiac failure and death must ensue.

EFFECTS OF VALVULAR LESIONS ON THE BODY GENERALLY.—Even when there is serious valvular disease compensatory hypertrophy may for a time suffice to carry on the circulation normally. But if, owing to undue strain, or, as usually happens, degeneration of the hypertrophied muscle occurs, compensation breaks down, dilatation once more gets the upper hand and is gradually transmitted backwards. First the left ventricle dilates (if the aortic valve be diseased), then the left auricle; the pulmonary system next becomes engorged, leading to dilatation of the right auricle. So far the lungs only will suffer, and engorgement, œdema, and dyspnœa occur. But the engorgement, if it still goes on, leads to dilatation of the right ventricle and incompetence of the tricuspid valve, and as soon as this ensues the whole systemic venous system becomes congested, and œdema and dropsy of the tissues, organs, and serous cavities is the final result, a train of events to which the name of "cardiac failure" or "back-pressure symptoms" is applied.

EFFECTS OF VALVULAR LESIONS ON THE PULSE.—All valvular lesions at first prevent the due filling of the vessels, and give rise to a small pulse. But as cardiac hypertrophy ensues the pulse may regain its normal volume. In aortic regurgitation a characteristic pulse is developed. Owing to the considerable cardiac hypertrophy the impulse is forcible, and the blood is driven with considerable force into the arteries and suddenly fills the vessels and imparts a marked shock to the finger. But owing to the regurgitation the arterial tone is not kept up, and the vessel as suddenly collapses. This is known as the "Corrigan" or water-hammer pulse.

DISEASES OF THE ARTERIES AND VEINS.

The arteries, particularly the aorta, are occasionally imperfectly developed and their walls abnormally thin (hypoplasia); this has occasionally been observed in hæmophilia. The arteries tend to atrophy in the course of wasting diseases.

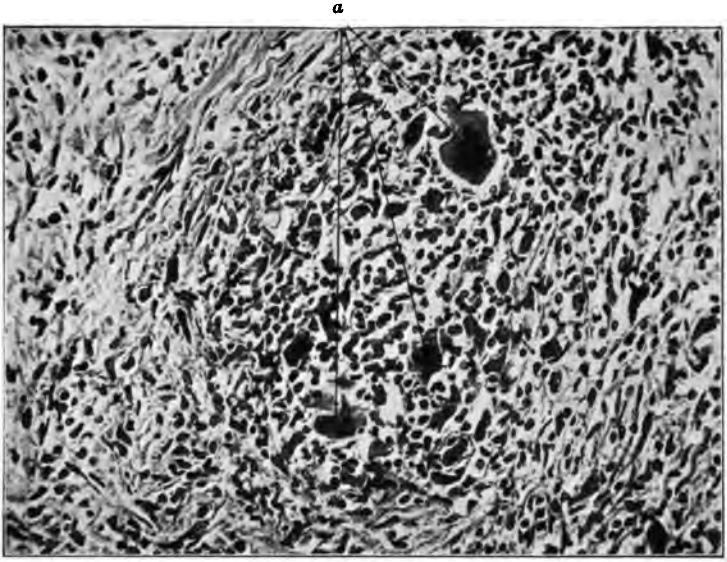
Fatty change is not infrequent in the deeper layers of the intima; lardaceous infiltration and hyaline degeneration occur, and calcareous infiltration of the larger vessels is common in arterial disease.

Hyperplasia of the arteries takes place when, after occlusion of a branch, the collateral circulation becomes established, and *hypertrophy* of the walls is the consequence of an increased arterial pressure.

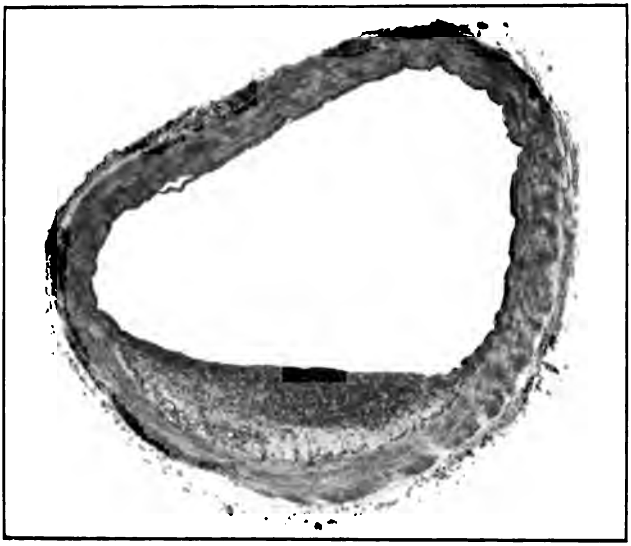
Acute arteritis is uncommon but may result from traumatism, extension, or arise in the course of certain infections. The intima becomes reddened and swollen, and the deeper layers and the media are infiltrated with leucocytes, in some cases terminating in pus-production (*suppurative arteritis*). Thrombosis frequently ensues, or dilatation or rupture.

Arteriosclerosis, also known as **atheroma**, arterio-capillary fibrosis, chronic endarteritis, and endarteritis deformans, is a chronic process, sometimes inflammatory, followed by degenerative changes and thickening of the arterial walls. The name has been applied in all probability to several distinct varieties of arterial disease. The condition may be circumscribed and local or diffuse and widespread. It generally occurs after middle life, and is frequent in the course of renal

PLATE XII.



A. Hodgkin's disease. Lymphatic gland showing the lymphadenoid cells, *a*. (Hæmatoxylin and eosin, × 120.)



B. Endarteritis (atheroma) of a cerebral artery. (Picrocarmine, × 25.)

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disease, alcoholism, syphilis, lead-poisoning, and other toxæmias.

Atheroma is a localised, patchy, fibro-plastic infiltration of the intima, and occurs mostly in the aorta and large arteries. At first there is a cellular and fibrinous infiltration of the deeper layers of the intima, which may undergo fibrosis and cicatrisation (Pl. XII., B.). Frequently the endothelium necroses and the infiltration, being soft and gelatinous, undergoes excavation, and an *atheromatous ulcer* is formed. Calcification is also a common event.

Intimal sclerosis is another variety. The entire intima becomes infiltrated with round cells with subsequent fibrosis. There is little tendency to necrosis, and the process results in a more or less uniform thickening all round the lumen, and it is relatively more frequent in the medium-sized and smaller vessels. This thickening of the intima is regarded by Thoma as compensatory and secondary to degenerative changes in the media.

Arterial hypermyotrophy is stated by Savill[1] to be of almost universal occurrence in some degree in persons past middle life. It consists in an increased thickness of the muscular tissue of the arteries, and is probably a genuine muscular hypertrophy. This condition is very frequent in chronic renal disease, as was pointed out by Johnson.

The simple muscular hypertrophy may continue as such for years, but is often succeeded by degenerative changes, focal necrosis, or widespread intimal and adventitial fibrosis and sclerosis, and occasionally calcification. The cause of the degeneration of the media is often primarily due to obstruction or obliteration of the vasa vasorum (Mott) and consequent defective nutrition of the muscle.

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[1] *Path. Soc. Trans.*, vol. lv, 1904, p. 375.

The mechanism by which renal disease brings about arterial hypermyotrophy is obscure. Johnson supposed that the toxæmia induced a contraction of the arterial muscle, which was followed by hypertrophy, and the narrowed arterioles raising the blood-pressure caused cardiac hypertrophy, particularly of the left ventricle, to overcome the increased resistance, and hence the cardiac hypertrophy of renal disease.

The focal necrosis of the hypertrophied artery Savill believes is largely responsible for cerebral hæmorrhage, dilatation, aneurysm, and rupture being the sequence of events.

Syphilitic arteritis chiefly affects the intima and adventitia. The deeper layers of the intima and of the adventitia are infiltrated with round and spindle cells, with subsequent fibrosis and thickening of the vessel wall, often to such an extent as almost, or quite, to obliterate its lumen. The media is but little altered or may be atrophied and fibrous. Syphilis may also induce arteriosclerosis, and gummata occasionally form in a vessel-wall.

Tuberculous arteritis may result from extension from a tuberculous process outside the vessel, from the presence of an infected embolus within the vessel, or by the direct implantation of bacilli carried by the blood on the vessel-wall. The latter occurs chiefly in the smaller arteries, particularly of the brain (in tuberculous meningitis). Small discrete tubercles develop, generally in the adventitia, and appear as greyish points. They may undergo caseation, with aneurysmal dilatation or rupture, or thrombosis or fibrosis may ensue and the vessel be partially or completely occluded.

Aneurysm.—An aneurysm is a more or less circumscribed dilatation of an artery. If the whole circumference of the vessel is involved, it is termed *fusiform*; if there is a pouching on one side, *saccular*;

if the vessel is dilated, elongated, and tortuous, *cirsoid*; if through rupture of the intima the blood passes between the coats of the vessel-wall, *dissecting*. If the blood escapes from the vessel but is confined in a sac formed by the surrounding tissues, this is a *false aneurysm*; if an artery and a vein communicate owing to some common wound, an *aneurysmal varix* is formed; and if between the two vessels an aneurysmal sac develops, the condition is known as a *varicose aneurysm.* Aneurysm almost always results from the effects of strain acting on a vessel the walls of which are degenerate, atheromatous, arteriosclerotic, etc. It is, therefore, frequent among those following laborious occupations and in the larger vessels, in which the blood-pressure is highest and degenerative changes commonest, and in those vessels, or parts of them, which are least supported by the surrounding tissues. In phthisical cavities in the lungs multiple aneurysms are frequently seen, due partly to loss of support and partly to erosion from without. Infective embolism may also cause inflammation and degeneration of the vessel-wall, followed by aneurysm.

The aorta, particularly the thoracic aorta, is the most frequent seat of aneurysm, after which follow the popliteal, femoral, carotid, and subclavian arteries.

In a recent aneurysm all three coats of the artery are present, but as dilatation proceeds the media tends to disappear and the intima and adventitia become thickened from a fibrous hyperplasia. Patches of atheromatous degeneration are generally present in, and a fibrinous deposit covers, the walls of the sac. This fibrinous deposit varies much in thickness, in some cases may almost fill the cavity, and is pale, dry, and laminated, the most recent layers next the blood being soft and dark. Extrême distension may ultimately lead to thinning of the walls and rupture.

An aneurysm may cause pressure on neighbouring parts, erosion of bone (but cartilage generally persists), and often obstruction of the circulation beyond. It may terminate in death by involvement of important structures, or most frequently by rupture, or may rupture into the tissues and form a false aneurysm, but in some instances by the deposition of fibrin a "cure," more or less perfect, occurs. The deposit of fibrin in such cases becomes more or less converted into fibrous tissue, but never completely so. Owing to the roughness of the interior of the aneurysm, a murmur can often be heard over it, generally systolic—*i. e.* during the onward flow of the blood.

Phlebitis, inflammation of the veins, may result from traumatism, extension from neighbouring parts, or infective material circulating in the blood. Gout is reputed to be a common cause. The coats of the vein become infiltrated with cells and the endothelium is raised and swollen; this frequently ends in thrombosis.

Varicose veins, dilated and tortuous veins, generally result from some impediment to the venous circulation. The veins are normally devoid of tonus, and the intravenous pressure is hardly appreciable, so that a slight obstruction to the onward flow is sufficient to cause distension and dilatation, which again reacts by rendering the valves impotent. The chief seats of varicose veins are in the lower extremity, where gravity is an important factor, in the hæmorrhoidal veins (piles), and in the spermatic veins (varicocele). Varicose patches of skin are liable to become inflamed from slight causes and to undergo necrosis, with the formation of the indolent *varicose ulcer.*

Phleboliths are calcareous masses formed by infiltration of an old thrombus with calcium salts.

CHAPTER XIV.

DISEASES OF THE RESPIRATORY TRACT.

GENERAL CONDITIONS AND DISORDERS AFFECTING RESPIRATION AND THE RESPIRATORY MOVEMENTS.

DISORDERS of the mouth, nose, and pharynx are not of great importance as affecting respiration. Post-nasal adenoids prevent nasal breathing, and necessitate mouth-breathing, and the air is neither filtered, moistened, nor warmed, and phonation is interfered with. When nasal breathing is interfered with, and mouth-breathing is therefore necessary, the mouth becomes dry and parched, particularly during sleep, and this is one of the causes of disturbed sleep. StClair Thomson and the writer also showed[1] that the nose fulfils an important function in freeing the air from dust and microbes. In persons the subjects of bronchial catarrh the warming of the air before inhalation into the lungs is important, and cannot be insured if there be nasal obstruction of any kind. Cleft-palate prevents simultaneous swallowing and breathing, and may lead to malnutrition in infants in consequence of the constant necessity for opening the mouth to breathe.

Pharyngeal conditions—*e. g.* enlarged tonsils, or pressure of an aneurysm—may interfere with respiration just as stenosis of the larynx or pharynx does. Loss of sensibility of the pharyngeal mucous membrane—*e. g.* during anæsthesia—and abolition of the cough reflex may lead to the inhalation of particulate infective matter, and the occurrence of an infective broncho-pneumonia, which is generally streptococcal. This explains the frequency of this condition after operations about the mouth, tongue, and throat, and as a prophylactic against which Cheyne has advocated the previous injection of anti-streptococcic serum. Paralysis of the muscles of deglutition and of the larynx, as in bulbar paralysis, similarly leads to the entrance of particulate infective matter into the lungs, and is often the direct cause of the fatal issue.

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[1] *Med.-Chir. Trans.*, vol. lxxviii, 1895.

The action of the ciliated epithelium is an important safeguard against the entrance of dust and microbes into the lungs. The action of the cilia is to propel such particles outwards, and hence below the larynx the respiratory mucous membrane is comparatively sterile. Up to a certain point the ciliated epithelium is able to expel the intruding particles; but should the dust be excessive some of it gains access to the lungs, and the various forms of pneumokoniosis result.

Coughing and *sneezing* are important defensive mechanisms, expelling particles, increased secretion, etc., but coughing if excessive is apt to lead to secondary pathological effects. Coughing tends to raise the blood-pressure; the violent expiratory effort accompanying it renders the intra-thoracic pressure positive and so obstructs the venous inflow into the thoracic venous trunks and heart and reacts backwards on the smaller veins and capillaries, which may rupture, producing ecchymoses. If the arterioles be diseased, coughing may lead to their rupture and the occurrence of apoplexy, probably on account of the heightened blood-pressure, caused by increase of peripheral resistance due to compression of the abdominal vessels by the contraction of the abdominal muscles during the paroxysm and increased force of the heart-beat to overcome this resistance. On the lungs coughing causes stretching and dilatation, followed by secondary changes resulting in emphysema (p. 306). Coughing if persistent may ultimately produce serious effects by interfering with rest.

Dyspnœa is a condition of forced breathing, usually with quickened respiration. It may involve both inspiration and expiration equally, or it may be mainly inspiratory as in laryngismus stridulus or mainly expiratory as in asthma. Practically, it is but a subacute form of asphyxia, and the forcible respiratory movements are due to the stimulation of the respiratory centre by an excess of carbon dioxide in the blood.

In cardiac disease, increased rapidity of respiration, shortness of breath (cardiac dyspnœa), is often a marked feature and seems in the earlier stages to be due largely to the interdependence of the cardiac and respiratory centres, as is shown by the constancy of the cardiac respiration ratio. In the later stages true dyspnœa supervenes and the normal cardiac-respiration ratio no longer obtains. This is due to engorgement of the lungs and deficient blood-aeration.

In renal disease a form of dyspnœa occurs, often paroxysmal, the pathology of which is uncertain. It may be caused by the circulation of toxic substances.

Dyspnœa in anæmia is due to the deficient oxygen-carrying power of the blood.

Orthopnœa is a form of dyspnœa in which the patient is compelled to sit up; it is often seen in pulmonary, and in the later stages of cardiac, diseases. According to

Lazarus Barlow,[1] the condition often supervenes suddenly and once developed usually advances. It is generally due to dilatation of the right ventricle, and the position assumed lessens the pressure of the abdominal viscera on the lungs and heart, and by gravity tends to empty the heart (Lazarus Barlow).

Cheyne-Stokes' respiration.—This consists in a periodic waxing and waning of the respiration. Commencing with shallow and infrequent respirations, these gain force until a condition almost of dyspnœa supervenes, when they again gradually die away and a pause ensues before the respirations recommence. It is most commonly and typically seen in renal disease. Filehne's hypothesis best explains it. This presupposes that there is from some cause a lessened irritability of the respiratory centre, so that it fails to respond to the stimulus of normal venous blood, hence the pause. The amount of carbon dioxide in the blood then goes on increasing until the stimulus is sufficient to occasion the response of the respiratory centre, and respiration recommences. The blood, however, which is thus arterialised by the respirations does not for a time reach the respiratory centre, and a condition of dyspnœa ensues which gives place to ordinary and then to reduced respirations when the arterial blood reaches the respiratory centre, this cycle being repeated again and again.

Mountain sickness is probably due to deficiency of oxygen. When the oxygen in air is reduced to about 10 per cent. dyspnœa and cyanosis commence, and it is at an elevation corresponding to a diminution of oxygen tension to about 10 per cent. that the symptoms of mountain sickness become evident.

Carbon monoxide replaces oxygen in oxyhæmoglobin and forms a stable combination with hæmoglobin which is useless for respiration. Air containing only 0·1 per cent. of this gas causes the blood to become half saturated—hence its extremely poisonous nature.

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[1] *Manual of General Pathology*, 2nd ed., 1904, p. 685.

Carbon dioxide acts partly by diluting the oxygen, but is also distinctly poisonous when the quantity exceeds about 5 per cent. In badly ventilated rooms the effects of the respired air are probably due, not so much to an increase of carbon dioxide and deficiency of oxygen, but to small quantities of organic substances (including, perhaps, traces of carbon monoxide) which are toxic, although Haldane and Lorrain Smith ascribe the effects solely to the excess of CO_2 and deficiency of O_2.

Chloroform has probably a direct action on the heart, though Lawrie and the Hyderabad Commission ascribe its fatal action to paralysis of respiration. Some of the fatal cases are the subjects of the lymphatic diathesis (see p. 244).

Certain general affections and conditions of the respiratory tract may now be considered.

SPASMODIC ASTHMA.—Spasmodic or bronchial asthma is a paroxysmal disease accompanied with expiratory dyspnœa. It commences suddenly, often in the early morning, and after lasting two or three hours gradually passes off, the patient frequently expectorating towards the close pellets of exceedingly tenacious mucus. The rate of respiration is but little altered, but the inspirations are shorter than normal, while expiration is greatly prolonged, and all the extraordinary muscles are brought into action. The lungs are manifestly over-distended during the attack. The pellets of expectoration contain Charcot-Leyden crystals and curious, twisted, fine threads or spirals—the *Curschmann's spirals.* Various theories have been advanced to account for this dyspnœic condition :

(1) That it is caused by a swelling of the bronchial mucous membrane as a result of hyperæmia.

(2) That it is due to a reflex spasm of the inspiratory muscles, particularly of the diaphragm.

(3) That it is a special form of bronchial catarrh (*bronchiolitis exudativa,* Curschmann).

(4) That it is due to spasm of the unstriped muscle of the bronchioles.

The last-named theory is the one which has most supporters at present, and some interesting researches by Brodie and Dixon confirm the idea that spasm of the bronchial muscles is the main cause underlying an attack.

The vagus is the motor nerve of the bronchial muscles, and by stimulation of the vagus in the rabbit and dog the amount of air entering the corresponding lung may be reduced to one fourth of the normal. In the cat both dilator and constrictor fibres are present in the vagus, and stimulation is usually followed first by a transient constriction, then by dilatation. It is difficult experimentally to obtain reflex constriction owing to the action of the anæsthetic, but stimulation of the nasal mucous membrane was frequently found to produce constriction if, instead of an anæsthetised, a decerebrate animal was employed. Reflex action probably plays an important part in the production of an attack of asthma in man—*e. g.* from over-loaded stomach and indigestion, odours, diseases of the naso-pharynx, etc. The sudden onset and rapid disappearance of the attack exactly corresponds with what is known to be the common course of a prolonged contraction of involuntary muscle. In an animal a typical asthmatic attack can be induced by giving a small dose of muscarine; the dyspnœa, distended thorax, and sibilant râles so characteristic of the disease are thus produced. Now, muscarine causes almost complete closure of the bronchioles by peripheral stimulation of the vagal endings. Brodie and Dixon[1] state as their general conclusions that true bronchial asthma is in all cases a spasmodic contraction of the bronchial muscles; that if it follows or occurs in an acute attack of bronchitis it has been reflexly produced, either from the bronchial mucous membrane or from some other hyper-irritable mucous membrane, or possibly from the combined action of the two abnormal surfaces acting on the medullary centre. The over-distension of the lung is the result of the bronchial spasm, and is produced because the action of filling the alveoli is always effected at a greater advantage than that of emptying, and that if extraordinary efforts at expiration are made they do but serve further to impede the emptying of the distended lung. The state of the thorax and the modified respiratory movements are the direct consequence of the over-distension and the spasm. The increased violence of inspiration is due to the great force required to get air through the constricted bronchioles, and the so-called inspiratory spasm is the evidence of the over-distension. The chest does not collapse, and therefore the respiratory muscles and ribs cannot fall into the true expiratory position, in which movements of small extent determine a considerable increase in capacity of the thorax. The violent movements observed consequently result only in a relatively small increase in capacity, and this in turn does not cause so large a fall in the alveolar pressure as would be produced by a similar volume increase in a less distended set of alveoli, because at the start the alveoli are well distended and filled with air practically at atmospheric pressure.

Diaphragmatic paralysis may be due to lesions of the cord at the level of the third and fourth cervical nerves, to compression of the phrenic nerve by tumour or aneurysm, or to a neuritis of the phrenic and its branches, which is usually diphtheritic.

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[1] *Path. Soc. Trans.*, vol. liv, 1903, p. 37.

THE RESPIRATORY ORGANS.

The respiratory tract consists of the nasal fossæ, the pharynx, the epiglottis, the larynx, trachea, and bronchi, and the respiratory organs proper, the lungs and pleuræ, which are enclosed within the thorax. The pharynx will be considered under the Digestive Tract.

The Nose.

The nasal fossæ are lined with a thick, vascular, mucous membrane, the extent of which is augmented by reduplications covering the inferior turbinates. The external nares are guarded by numerous hairs (vibrissæ) and the epithelium just within and covering the cartilages is tessellated. Behind this the mucous (Schneiderian) membrane is stratified and covered with columnar ciliated epithelium and contains numerous compound racemose mucous glands. The deeper layers of the mucous membrane are plentifully supplied with capillaries, lymphatics, and lymphoid tissue, the latter forming small masses, the solitary glands or follicles.

Malformations.—The nose may be absent, particularly in monsters. The commonest malformation is deflection of the nasal septum. Clefts in the alæ nasi also occur.

RHINITIS, inflammation of the nasal mucous membrane, is common.

Catarrhal rhinitis.—This is the ordinary *coryza* or cold in the head. The mucous membrane is hyperæmic and swollen, the mucous glands secrete actively a serous, sero-mucous, or sero-purulent secretion containing much mucus, desquamated epithelial cells, and leucocytes or pus-cells. *Hay fever* is an acute catarrhal rhinitis and conjunctivitis caused by the pollen of various grasses.[1]

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[1] See Glegg, *Journ. of Hygiene,* vol. iv, 1904, p. 369.

Hypertrophic rhinitis is a chronic condition associated with displacement of bones, foreign bodies, polypus, syphilis, etc. The mucous membrane is hyperæmic and much thickened, the inferior turbinates are frequently enlarged, and the lymphoid nodules increased in size.

Atrophic rhinitis.—In this the mucous membrane undergoes atrophy, the exudation is scanty and forms crusts, ulcers are frequently present, and the secretions decompose and generate horrible fetor (*ozæna*). It is a chronic and almost incurable condition, the ætiology of which is unknown. Various micro-organisms have been found, including diphtheritic forms, but none can be considered to be specific.

Membranous rhinitis is characterised by the formation of a well-marked false membrane. It is generally diphtheritic in nature, virulent diphtheria bacilli being present.[1] It differs from nasal diphtheria, the extension of a pharyngeal or laryngeal diphtheria to the nose, by being chronic and usually unaccompanied with marked constitutional disturbance.

Tuberculous rhinitis, which is rare, may occur in the form of a deposit of tubercles which subsequently caseate and ulcerate, or as a lupus. Lupus not infrequently attacks the nose externally, completely destroying it, and leading to a hideous deformity, one variety of the "king's evil."

Syphilitic rhinitis may occur as a catarrh, or may be associated with the formation of gummata with much destruction of bone and cartilage, causing sinking in of the bridge, a characteristic syphilitic lesion. Syphilitic ozæna is not uncommon. In some instances the soft parts of the nose become completely destroyed, another variety of the "king's evil."

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[1] See Lack, *Med.-Chir. Trans.*, vol. lxxxii, 1899, p. 1.

Leprosy is very common in the nose; in fact, it is generally the first place to be attacked. Nodules form which subsequently ulcerate, and the secretion contains numbers of bacilli.

Glanders is rare in the nose; nodules form and ulcerate.

TUMOURS OF THE NOSE.—The commonest tumour is the *nasal polypus,* most frequently developing from the middle turbinates. It is soft and gelatinous, and is generally pedunculated, and consists microscopically of a delicate areolar tissue enclosing in its meshes a serous fluid (Pl. I., A.). It is frequently described as a *mucous* polypus but is generally in reality an œdematous fibroma; true mucous polypi are of rare occurrence. In some instances the structure is *glandular,* the adenomatous polypus, occasionally it is *angeiomatous.*

Sarcoma and *carcinoma* are rare as primary growths, though they frequently invade the nose from neighbouring parts.

Rhinoliths are calcareous concretions generally deposited on dried crusts or foreign bodies.

The Larynx.

The epiglottis consists of yellow elastic cartilage and is covered with a stratified tessellated epithelium, except at its base, where the epithelium is columnar ciliated. The vocal cords are also covered with the former variety of epithelium. The greater part of the cricoid, thyroid, and arytenoid cartilages are composed of hyaline cartilage, which is prone to ossify as life advances. The larynx from the level of the vocal cords downwards is covered with a columnar ciliated epithelium, by the vibratory action of which the mucus, etc., is propelled upwards. The cartilages are actuated by striated muscle. All the intrinsic muscles of the larynx are supplied by the inferior or recurrent laryngeal branch of the vagus with the exception of the crico-thyroid, which is supplied by the external branch of the superior laryngeal.

Malformations are very rare.

Paralysis of the intrinsic muscles of the larynx is not uncommon. It may be due to central causes, being met with in the course of bulbar paralysis and multiple sclerosis, or to peripheral disease involving the trunk of the vagus or the recurrent nerve, such as tumours in the neck, and particularly aneurysm of the innominate on the right side and of the aorta and mediastinal growths on the left. Paralysis of all the muscles supplied by this nerve leads to immobitity of one or both vocal cords, according as the disease is uni- or bi-lateral, the cord occupying a position midway between phonation and inspiration, but there is no dyspnœa. Incomplete paralysis almost always involves the posterior crico-arytenoid muscle, which is the abductor of the cords, leading to adduction of the cords, and if bilateral, to stridor and intense dyspnœa. It would seem as if the abductor fibres are more vulnerable than the adductor, and hence the former may suffer, while those of the adductors escape. Generally also, as in the limbs, there is a greater proneness for the abductors to suffer in the course of paralysis than for the adductors to do so. A paralysis *limited* to the adductors is generally functional. Loss of voice is known as "aphonia."

LARYNGISMUS STRIDULUS, "child crowing," occurs in young children, and is characterised by inspiratory dyspnœa. It probably includes several different conditions—*e. g.* pure spasm of the glottis, a slight degree of catarrhal laryngitis, etc. It appears to the writer that in many of the cases a slight catarrh with subsequent *drying of secretion,* together with the smallness of the child's glottis, is a sufficient explanation of the attack. Enlarged thymus has also been considered to be a cause (thymic asthma).

INFLAMMATION, known as "laryngitis," is frequent.

Acute laryngitis occurs as the result of cold, traumatism, inhalation of irritating vapours, etc. The mucous membrane is hyperæmic, the epithelium partially desquamated, and increased secretion of a mucous or muco-purulent character is present; if severe, ulcers may form, particularly on the vocal cords and posterior commissures. In some cases the inferior surface of the epiglottis and aryteno-epiglottic folds and other parts of the mucous membrane become infiltrated with a serous exudation which may produce death by suffocation by closing the glottis—acute *œdema of the glottis.* This must be distinguished from chronic œdema the result of chronic pulmonary, cardiac, or renal disease. Acute œdema may sometimes occur in the course of cancer, tubercle, syphilis, and diphtheria.

Chronic laryngitis may be a sequel of an acute attack or may be chronic from the first. It is frequently met with in singers, lecturers, political speakers, etc., whose vocation requires constant use and often strain of the voice (clergyman's throat). The changes are dilatation of the vessels, with either atrophy or hypertrophy of the mucous membrane, the epithelium of which may be abraded or altered.

On the vocal cords of singers and others nodular thickening of the epithelium frequently occurs (singer's node).

Diphtheritic laryngitis is one of the commonest lesions of diphtheria, sometimes primary but often secondary to pharyngeal diphtheria. A tough, yellowish, wash-leather-like pseudo-membrane forms more or less extensively over the larynx, in some instances forming a perfect mould of the organ. The membrane consists of fibrin with entangled leucocytes and numerous diphtheria bacilli, and the surface of the mucous membrane undergoes coagulative necrosis. If the membrane be detached, it leaves an abraded, raw surface.

Membranous laryngitis, not diphtheritic, may occasionally be caused by the pneumococcus, the streptococcus, and perhaps other micro-organisms, and also results from the action of boiling water or steam, or irritants such as chlorine, ammonia, and strong acids. Clinically it resembles the diphtheritic.

Specific fevers frequently affect the larynx. In typhoid the mucous membrane may be infiltrated with round cells which often ulcerate. In variola a like infiltration, simulating pustules, may occur.

Tuberculous laryngitis.—Tubercle frequently attacks the larynx, and is generally secondary to pulmonary tuberculosis, rarely primary. It usually commences with the formation of miliary tubercles at the margins and under-surface of the epiglottis, and on the vocal cords near the posterior fissure. The tubercles increase in size, caseate and ulcerate, and the whole thickness of the mucous membrane and the cartilages may be involved. The disease may spread to other parts of the larynx, and great destruction and deformity may result. In rare instances, the tubercles, instead of caseating, may undergo fibroid induration and form nodular masses. *Lupus* and *leprosy* may also occur in the larynx.

Syphilitic laryngitis is common. It may occur as a simple catarrh, as mucous patches (rare), but most commonly as ulcers secondary to gummata. These are generally situated on the epiglottis, vocal cords, or posterior wall, and are sharply circumscribed and deeply excavated, and may extend to the cartilage.

TUMOURS are frequent in the larynx. The commonest is the *papilloma*, which may be single or multiple, and varies in size from a pin's head to a cherry. *Fibroma* and *angeioma* also occur, also *adenoma* (derived from the glands), *mucous polypus* (usually an œdematous fibroma), and rarely others.

Carcinoma is not infrequent, and the larynx is one of the sites in which it may occur in young adults. It is usually of the squamous-celled type. *Sarcoma* is much less frequent than carcinoma. *Chondritis* and *perichondritis* are almost always secondary to conditions already described, particularly tubercle, syphilis, and carcinoma. The articulations may be affected with osteo-arthritis, and ankylosis may occur.

The Trachea and Bronchi.

The trachea and primary bronchi are composed of incomplete rings of hyaline cartilage, the openings in the rings being bridged over with fibrous tissue and non-striated muscle. The mucous membrane is stratified, the free surface being covered with a layer of columnar ciliated epithelium. In the smaller bronchi the cartilage exists in the form of small irregular plates; in the smallest it is altogether absent, and a distinct layer of non-striated muscle is present. The epithelium also becomes reduced to a single layer of columnar ciliated cells, and finally, to a basement membrane covered with flattened pavement cells, the change first occurring in the respiratory bronchioles near the passage to the infundibula, where groups of pavement cells appear among the columnar ciliated ones.

Malformations are rare. The trachea may divide high up, or may end blindly. A communication may exist between the *œsophagus* and *trachea* near the bifurcation. Absence or fusion, and longitudinal or transverse cleavage, of the rings are less common. A not infrequent malformation is a fistula of the trachea (*branchial fistula*) opening in the neck, usually just at the inner border of the sterno-mastoid and a little above the sterno-clavicular articulation. It is due to failure of union of the third and fourth visceral arches of the embryo (branchial clefts). By occlusion of the fistula or incomplete closure of a branchial cleft a cyst may result (*branchial cyst*).

TRACHEITIS (inflammation of the trachea) is generally associated with laryngitis or bronchitis, and has the same characters as the latter (see below).

Tubercle, syphilis, and *tumours* of the trachea are rarely primary. Secondary carcinoma may extend from the œsophagus.

BRONCHITIS (catarrhal inflammation of the bronchi) may affect the medium-sized bronchi, constituting the ordinary bronchitis, or the smaller bronchi or bronchioles, capillary bronchitis. According to Hamilton, bronchitis commences with a dilatation of the blood-vessels in the inner fibrous coat of the bronchi; the basement membrane then becomes œdematous, thickened, and thrown into folds, and after twenty to thirty hours the columnar epithelium becomes loosened and desquamates in patches, and the bronchial mucosa appears red, from congestion, instead of grey. The congestion may spread and involve all the vessels in the walls of the bronchi, which become more or less infiltrated with leucocytes. In place of the columnar cells which have desquamated various rounded, elongated, and irregular transitional cells, embryonic in type, often accumulate on the basement membrane, and, being cast off, constitute the main portion of the cellular elements of the secretion. At the same time the mucous glands are congested, the epithelium lining their ducts partly desquamates, and an abundant secretion of mucus ensues, which, with the cells before mentioned, constitutes the bronchial expectoration. The lymph-glands at the root of the lung are invariably enlarged and congested. Resolution takes place by subsidence of the congestion of the mucous membrane and re-formation of the normal epithelial covering. In some instances, probably as a result of infection with putrefactive organisms, and particularly when bronchiectasis is present, the expectoration and breath may become very offensive, "fetid bronchitis."

Bronchitis may be caused by any irritant substance, gaseous or particulate, and many species of micro-organisms have been isolated in various cases, but none is specific. An eruption of tubercles around bronchioles is common in phthisis, and causes a "tuberculous bronchitis."

Croupous bronchitis is characterised by a fibrinous exudation, which, on coagulation, forms a membrane on the walls of the bronchi, and may extend into their minutest ramifications. It is generally diphtheritic in nature, though occasionally irritants, such as acids and boiling water or steam, may produce a fibrinous exudation and membrane in the larger tubes.

Fibrinous or plastic bronchitis is a rare disease, characterised by the occasional expectoration of fibrinous casts of the bronchi. Fine spirals (Curschmann's spirals) and Charcot-Leyden crystals are generally present in the casts. The ætiology is unknown.

Chronic bronchitis.—This may arise from a succession of attacks of the acute disease, or may be chronic from the first, and is then usually associated with chronic cardiac or renal disease, gout, emphysema, etc. The mucous membrane is congested and thickened, the epithelium is more or less shed, and the tubes contain a yellowish muco-purulent secretion. The vessel-walls are frequently thickened, the muscular coat of the bronchi either atrophied or hypertrophied, and the lungs generally emphysematous. More or less bronchiectasis is frequently present.

BRONCHIECTASIS.—By this is meant a permanent dilatation of the bronchi. The dilatation may be irregular or cylindrical, sometimes fusiform, less frequently saccular. It is commonly associated with fibroid induration of the lung, the result of tubercle or syphilis, and the cavities in this form are irregular. The explanation of the dilatation is as follows: The newly-formed fibrous tissue, as is always the case, contracts, and, lying as it does between neighbouring bronchi, tends to draw their walls towards one another—*i. e.* tends to dilate their cavities. This force, however, would only cause contraction of the whole lung (*cf.* Cirrhosis of the Liver) were it not for the fact that the surfaces of the lungs are kept attached to the chest-walls by the pleurisy which invariably accompanies the fibroid induration. The lung tissue between the bronchi contracts, and in consequence the cavities of the bronchi must become enlarged and dilated. Changes in the walls of the bronchi, whereby they become atrophied and less rigid, conduce to the dilatation. Bronchiectasis also arises in connexion with emphysema, and is merely an extension of that condition. It may likewise occur in pulmonary collapse, and is then compensatory owing to the increased pressure brought to bear on the patent bronchi. The walls of a bronchiectasis frequently ulcerate, and this may lead to rupture and pneumo- or pyo-pneumo-thorax. The contents of the cavity are a muco-pus, which may be horribly offensive and communicate its fetor to the breath.

Syphilis and *tumours* are rare. *Bronchial calculi,* consisting of inspissated inflammatory deposits, incrustations on foreign bodies, etc., occasionally occur.

The Lungs.

The smallest bronchi terminate in infundibula, the walls of which are sacculated and form the alveoli or air-cells. These measure about 0·5 mm. in diameter, and are lined with large, thin, irregular endothelial cells, with here and there small, flat, polygonal cells between them, which rest on a fibrillated connective-tissue with coiled elastic fibres, forming the walls of the alveoli. In these a network of capillary vessels ramify, forming a single layer, uniting the branches of the pulmonary artery and vein. There is also a separate blood-supply to the structures of the lung through the bronchial vessels. A few granular, rounded, amœboid cells are usually found free in the air-cells and smaller bronchioles, and frequently contain carbonaceous particles. They may migrate into the pulmonary tissue and thence into the lymphatics and bronchial glands.

The right lung is the larger and weighs on an average 680 grams in the male, the left 600 grams, with a normal variation of 60–70 grams above or below these weights. Each lung of the female is some 150 grams lighter than the corresponding one of the male. When pressed between the fingers, the lungs impart a crepitant sensation, which is accompanied by a peculiar noise. On cutting into the lung, the same noise is heard, and a small amount of frothy, reddish, fluid exudes. The lungs are very elastic, and on opening the thorax shrink to about one third of their volume. The normal lung always contains air and floats in water, its specific gravity being 0·35–0·75. In the fetus the lungs contain no air and consequently sink in water, the specific gravity of the pulmonary tissue without air being 1·06. The condition of unexpanded lung containing no air, as met with in the stillborn, is known as *atelectasis.* The right lung is divided by two fissures into an upper, a middle, and a lower lobe; the left lung has only a single fissure, and is divided into upper and lower lobes. The nerve-supply is derived from the anterior and posterior pulmonary plexuses, which are chiefly formed of branches from the vagus, joined by others from the sympathetics.

The respiratory act occurs about 16 or 17 times a minute. Some 300 c.c. of air pass in and out with every respiration. The expired air is nearly saturated with moisture, and contains 4·4 per cent. of CO_2, 16·6 per cent. of O_2, and 79 per cent. of N_2, by volume. Owing to their elasticity, the lungs are always tending to collapse, and a negative pressure amounting to 6–30 mm. of mercury is thereby created within the pleural cavity.

Malformations of the lung are rare. Occasionally variations in the arrangement and number of the lobes occur.

ATELECTASIS has already been referred to. It is the condition of unexpanded lung such as is present in the fetus and stillborn. In this case it is complete and general, but it may occur in infants as local patches owing to obstruction—*e. g.* mucus—in some of the bronchi, preventing inflation.

COLLAPSE is a condition in which the air is partially or completely driven out of portions of the lung. It occurs from (*a*) pneumo-thorax, air or gas in the pleural sac; (*b*) fluid in the pleural sac, serum, pus, or blood, compressing the lung (from these two causes a whole lung may become collapsed); (*c*) bronchial obstruction—*e. g.* by viscid mucus. This acts as a ball-valve, air escapes during expiration, but during inspiration the plug is driven backwards and prevents inflation of the area supplied by the bronchus. Even without this ball-valve action, if a bronchus be plugged, the air is gradually absorbed from the alveoli behind the plug, the oxygen first being removed, then the CO_2, and finally, the nitrogen. (*d*) Lastly, rupture of air-vesicles by forced expiratory effort—*e. g.* in whooping-cough—leads to collapse. Collapsed lung is dark red in colour and congested, and hæmorrhages may be present; it is non-crepitant, and sinks in water. For a time, if the cause be removed, the collapsed area may be re-inflated, but later this becomes impossible, fibrous hyperplasia takes place, atrophy of the alveolar endothelium ensues, the apposed walls of the alveoli unite, and a pale, shrunken patch of leathery consistence is the result.

EMPHYSEMA.—This is a condition in which the lung is over-distended with air. There are two varieties, the interstitial, which is rare, and the vesicular or pulmonary, which is one of the commonest of pathological alterations of the lung.

Interstitial emphysema usually occurs when the lung is wounded by a spicule of bone—*e. g.* in broken rib—the air then making its way into the interstitial tissue. It is of little importance.

Vesicular emphysema may be local or more or less general. Individual air-sacs become distended, the distension commencing in the infundibula; their walls become thinned and rupture, and intercommunication takes place, so that a cavity corresponding to several alveoli is formed. In extreme cases, several of such cavities may fuse, and emphysematous blebs or bullæ form on the pleural surface. The chest in marked emphysema is enlarged antero-posteriorly so that it becomes barrel shaped, the chest-wall is frequently rigid, moves as a whole up and down, does not distend during inspiration, and the superficial veins are frequently enlarged. On opening the chest, the lungs do not collapse to anything like the normal extent, owing to loss of elasticity, and indeed often bulge. The apices and anterior margins are the seats of most marked emphysema, the lungs being less supported in these situations, and the lungs may overlap the heart so as completely to obscure the cardiac dulness. The emphysematous parts are pale grey, and dry, and impart a peculiar soft feel to the touch. The heart is frequently dilated and hypertrophied. Microscopically, owing to loss of septa and fusion of air-cells, the normal alveolar structure is obliterated, and single large air-spaces are formed, while chronic bronchial catarrh, and interstitial changes with bronchiectasis, are frequently present. In some cases there is great destruction of capillaries and consequent interference with the pulmonary circulation.

Various theories have been advanced to account for the general or diffuse variety. Laennec and Gairdner suggested that it is the result of forced inspiratory efforts, particularly when the glottis is closed. The *expiratory* theory of Jenner and Mendelssohn, which is that generally held at present, ascribes the condition to violent expiratory efforts with closed glottis, as in coughing, glass-blowing, and playing wind instruments, straining, etc. This factor is doubtless aided by nutritive changes in the alveolar walls, due to chronic bronchial catarrh, etc., which is so commonly present. Although generally a disease of adults after middle life, it may occur in children, particularly after whooping cough and measles.

Local emphysema is generally compensatory to a local collapse. Should one lung become collapsed, the other may dilate vicariously.

ACUTE CONGESTION occurs in the primary stages of acute inflammatory diseases of the lung, after the inhalation of irritant gases, and from toxic substances circulating in the blood, extensive burns, etc. The lung is swollen, dark in colour, firmer than normal, engorged with blood, and on incision a quantity of sanguinolent, frothy, fluid escapes. The capillaries are dilated and some amount of exudation, with a few chromocytes and other cells, occupies the air-cells. A zone of local hyperæmia surrounds an infarction.

Chronic congestion is much more frequently seen than acute congestion. It occurs whenever the circulation through the lung is impeded—*e.g.* in chronic heart-disease, diseases of the lung impeding the blood-flow, as emphysema and interstitial fibrosis, also when the heart and circulation are weak, as in cachectic states, long-continued fevers, etc.; the latter is often termed *hypostatic congestion* or *pneumonia* and is one of the commonest post-mortem conditions. In the more acute form, the bases of the lungs are particularly affected; they are darker and firmer than normal and heavy, so that pieces may sink in water, the air-cells being occupied by a sanguinolent exudation. The more chronic form associated with chronic cardiac disease is characterised by an increase in the interstitial tissue, capillary dilatation, exudation of fluid containing large catarrhal cells, many of which are pigmented, and chromocytes, into the alveoli, and deposition of pigment, which gives the lung a brownish colour, and the condition has, therefore, been termed *brown induration.* Hæmorrhages and pleuritic adhesions may occur, together with congestion of the bronchi and enormous dilatation of the capillaries in the bronchial walls.

Anæmia of the lung may occur in general anæmia, or locally in embolism of the pulmonary vessels, pressure of tumours or pleuritic effusion, etc.

Œdema of the lung is very frequent, particularly in chronic cardiac disease. A certain amount of œdema also occurs in acute inflammatory affections of the lung; it may be general or local. When large areas of lung-tissue are involved, the part is enlarged and boggy to the feel, heavy, and on incision a large quantity of frothy, slightly blood-stained fluid escapes.

Hæmorrhage of the lung may occur by diapedesis or by rhexis. In infective diseases, inflammation, circulatory disturbances, asphyxia, purpura, etc., punctiform hæmorrhages occur. Larger hæmorrhages may result from erosion of vessels in tubercle and cancer, rupture of small aneurysms in tuberculous cavities, rupture of an aneurysm, etc.

Infarction generally results from embolism of the branches of the pulmonary artery, the emboli being derived from thrombi in the systemic veins or right heart. It occurs as a pyramidal mass with the base at the pleural surface, on which there may be a fibrinous deposit, swollen, dark plum in colour, and fairly sharply defined from the surrounding hyperæmic lung-tissue, and varies in size from a pea to an egg. If the embolus be infective, an abscess results. (Hamilton,[1] however, is of opinion that the greater number of instances of so-called hæmorrhagic infarction of the lung have nothing to do with embolism. He ascribes the condition generally to rupture of capillaries which are in a state of chronic distension, the wedge shape being due, not to the distribution of the terminal branches of the pulmonary artery, but to the shape of the terminal bronchus and attached air-vesicles in which the blood is confined.)

Gangrene of the lung is always secondary and due to infection, and may occur in traumatism, pneumonia, bronchiectasis, tubercle, and cancer, perforation of the œsophagus, inspiration of putrid matter from the upper air-passages, gangrenous inflammation of the larynx, etc., and infective embolism; in certain cases in debilitated alcoholic subjects it may arise without obvious cause. The condition may be circumscribed, an area breaking down, leaving a cavity which is frequently encapsuled and tends to heal, or widespread or diffuse, particularly after pneumonia. It is characterised by the expectoration of dark sputum having an extremely fetid odour.

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[1] *Text-Book of Pathology*, vol. i, p. 685.

An amœbic or other abscess of the liver may rupture into the lung.

PNEUMOKONIOSIS.—This is a condition induced by the inhalation of dust particles—coal dust in miners (*anthracosis*), metallic dust, usually iron oxide, in grinders (*siderosis*), stone dust, etc., in masons, grinders, potters, etc. (*lithosis*). The result varies with the kind of dust, the stone and metal dusts being most injurious, coal dust less so. Irritative changes with bronchial catarrh are set up, together with marked hyperplasia of the connective tissue, resulting in fibrosis and induration, sometimes in the form of scattered nodules, sometimes as a general fibrosis, the lesions being most marked at the apices. Pleural adhesions are often present and extensive. The particles inhaled are taken up by the leucocytes and deposited in the lymphatics, so that the particles may be detected microscopically, and in the case of anthracosis give rise to marked black pigmentation. Secondary tuberculous infection is frequent.

CATARRHAL PNEUMONIA.—This form of pulmonary inflammation, also known as broncho- or lobular pneumonia, frequently occurs as the result of the inspiration of any irritating substance, particularly of blood and septic material in operations about the mouth and upper air-passages, in the course of many infective diseases—*e. g.* influenza, typhoid, plague, measles, and whooping-cough[1]—and may be caused by the causative organism of the infection, such as the influenza, typhoid, and plague bacilli, or by the streptococcus or the pneumobacillus of Friedländer. In old people suffering from various diseases, owing to lowered vitality, very mild irritants seem to be able to induce the disease.

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[1] Of course a true croupous pneumonia (see below), due to secondary infection with the *Diplococcus pneumoniæ*, may occur in the course of any disease.

This form of pneumonia is localised more or less to the area of distribution of the bronchioles, and therefore appears as scattered patches (hence the term "lobular"), which may, however, if close together, coalesce and involve large portions of the lung.

The appearance of the lung varies considerably with the stage and extent of the disease. In the early stage the lung is hyperæmic, and numerous small, greyish-yellow areas encircling bronchioles, which appear as minute dots at the centres, can be seen, and reddish areas of consolidation, which feel solid to the touch, may be present. Later, when the extent of involved lung has increased, the organ may have a marbled appearance from the presence of alternating areas of hyperæmic, consolidated, collapsed, and emphysematous portions of tissue.

Microscopically, the interalveolar capillaries are dilated, the submucous tissue is infiltrated with round cells, and the alveoli are filled with cells—partly leucocytes, but mostly large and round or ovoid, with spheroidal nuclei, which are desquamated epithelial cells (Pl. XIII., A.). Around the consolidated patches there may be hyperæmia, or collapse, or compensatory emphysema.

Resolution is brought about by the absorption and expectoration of the contents of the alveoli. In some cases resolution may be incomplete, and the interstitial cells may become organised and fibroid induration is the result. In old persons, and in those suffering from chronic cardiac or renal disease, the dependent parts of the lung are liable to be attacked with catarrhal pneumonia, which under these circumstances has received the name of "hypostatic pneumonia."

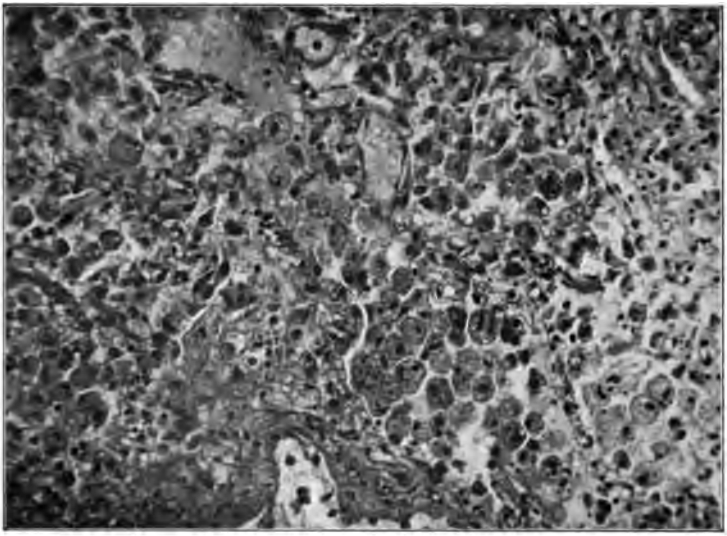
ACUTE CROUPOUS PNEUMONIA.—This is the ordinary form of "inflammation of the lungs," and is also known as lobar pneumonia. It is an acute specific general disease caused by the *Diplococcus pneumoniæ* or Fraenkel's pneumococcus (p. 129), with almost always local manifestations in the lung, the pneumonia, and is characterised by sudden onset, high fever, and in favourable cases termination by crisis about the sixth to the ninth day. The right lung is more frequently attacked than the left in the proportion of about five to three, and the lower lobes are more frequently attacked than the upper, but both lungs may be affected. The pathological condition may be described in four stages:

(1) *Congestion.*—The interalveolar capillaries are enlarged and dilated, and may project into the alveoli, which contain an excess of reddish serous fluid, with a few chromocytes, leucocytes, and desquamated epithelial and endothelial cells.

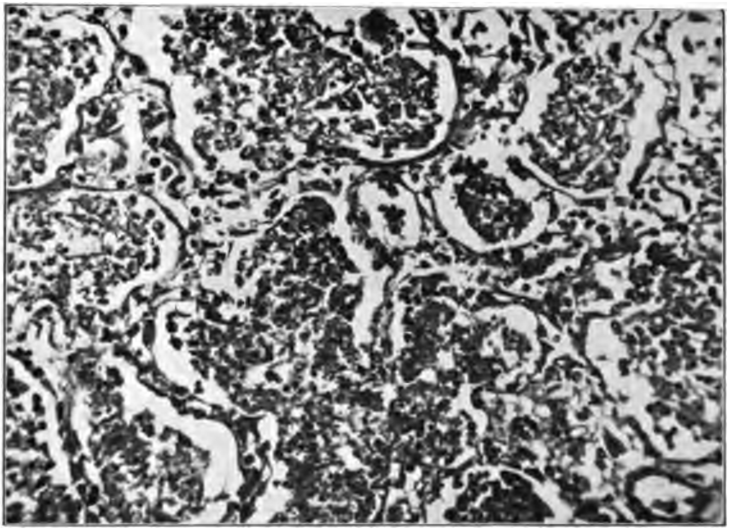
The lung is enlarged, dark red, firmer to the touch and crepitates less than normal, and exudes a frothy, reddish serous fluid on pressure. Its specific gravity is increased, but it still floats in water.

(2) *Red hepatisation.*—Exudation into the air-cells continues, the exudation coagulates, and the alveoli become filled with coagula, consisting of fibrin, entangling a large number of chromocytes, though a few leucocytes and desquamated cells can still be seen (Pl. XIII., B., and Pl. XIV., A.). The lung is enlarged, solid, and heavy, and dark-red in colour, like the liver, hence the term "hepatisation," and it sinks in water. A viscid mucus may be expressed from the bronchi, and on scraping the cut surface of the lung, the contents of

PLATE XIII.



A. Catarrhal pneumonia. The alveoli are filled with large "catarrhal" cells. (Hæmatoxylin and eosin, × 120.)



B. Acute croupous pneumonia; stage of red hepatisation. (Hæmatoxylin and eosin, × 85.)

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the air-cells appear as minute fibrinous plugs on the blade of the knife. Pneumococci are present in the alveoli in large numbers, many of them being within the leucocytes. In all cases the interalveolar septa are œdematous and infiltrated with round cells.

(3) *Grey hepatisation.*—The stage of red hepatisation slowly subsides, the hyperæmia disappears, and the fibrin and chromocytes are gradually liquefied and got rid of. This period of softening is characterised by a large accumulation of leucocytes in the air-cells, and this event, together with the removal of the chromocytes and the subsidence of the hyperæmia, causes the lung to assume a greyish colour (Pl. XIV., B.). Both red and grey hepatisation may exist in adjacent portions of the affected lung. The lung is still enlarged and solid, and sinks in water, but is softer than in the red stage.

(4) *Resolution.*—The advent of grey hepatisation marks the commencement of resolution. The exudate softens, and is partly expectorated, partly absorbed by the lymphatics, and partly carried off by the leucocytes. In favourable cases the lung returns to normal, and recovery is complete in from two to four weeks.

The bronchi are always inflamed in the pneumonic area, and contain a reddish, viscid exudate. The expectoration is characteristic, being an extremely viscid mucus, brownish-red in colour (the "rusty sputum"), containing a few leucocytes and catarrhal cells, numerous chromocytes, and large numbers of the specific organism in the form of encapsuled diplococci. The pneumococci can in many cases be found in small numbers in the blood of the general circulation. The pleura adjacent to the pneumonia is always inflamed, thickened, and opaque, has on its surface a fibrinous exudate, more or less pleuritic effusion is present, and the bronchial glands are swollen and inflamed. The urine frequently contains a little albumen, and is characterised by an almost complete absence of chlorides during the height of the diseases. Herpes frequently appears on the lips and alæ nasi.

Pericarditis, endocarditis, and meningitis (due to the pneumococcus) are frequent complications. Acute croupous pneumonia occurring in the course of other diseases—*e. g.* typhoid, influenza, etc.—is always due to secondary infection with the pneumococcus. The disease, instead of ending in resolution and recovery (which is the rule in healthy young adults), may have various other terminations. The condition of grey hepatisation may become extreme, the leucocytes very numerous, and abscess of the lung result. Gangrene is another event; the pneumonic process may so interfere with the vitality of the tissues that necrosis ensues, particularly if interstitial hæmorrhages have occurred, which is frequently the case in certain malignant forms of the disease. Sometimes the disease, instead of progressing to recovery, becomes chronic, and is followed by induration. Cellular infiltration and proliferation in the interstitial tissue becomes extreme, and is followed by fibrous hyperplasia, which may lead to obliteration of some of the alveoli, emphysema, bronchiectasis, etc., and the pleura may become thickened and adherent.

In unresolved pneumonia the exudate in the alveoli is often dense and hyaline and poor in cells. The softening and liquefaction of the exudate is largely due to a process of autolysis, caused by ferment action.[1] In the stage of grey hepatisation autolysis takes place quickly and perfectly, while in that of red hepatisation it is very imperfect. Flexner, therefore, believes that non-resolution in croupous pneumonia is due to failure of autolysis of the exudate, either because of some disproportion between the leucocytes and other constituents or from some other cause as yet unknown, resulting in non-absorption, and followed by organisation.

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[1] See Flexner, *University of Pennsylvania Med. Bull.*, July, 1903.

VAGUS PNEUMONIA.—It has been observed that section of the vagus in animals is very frequently followed by pneumonia of the croupous type. It is probably due to paralysis of the larynx and entrance of foreign matter.

CHRONIC INTERSTITIAL PNEUMONIA.—This clinical variety of the disease, which is characterised by great increase in the interstitial tissue and fibrosis, is pathologically of several forms. It may be secondary to acute croupous pneumonia, may occur locally after collapse or infarction, may arise peri-bronchially associated with chronic bronchitis, may be a consequence of chronic pleurisy, or be tuberculous or syphilitic, or a pneumokoniosis.

PLEUROGENIC PNEUMONIA.—This is a pulmonary inflammation secondary to pleurisy. In all cases of pleurisy the contiguous lung is involved. It tends to be interlobular, perivascular, and peribronchial, and may be suppurative.

HÆMATOGENOUS PNEUMONIA.—This is the result of infective embolism, and occurs in pyæmia and other infective diseases. The inflammation is of the catarrhal type and frequently ends in suppuration.

Tuberculosis of the Lung.

Tuberculosis of the lung, tuberculous phthisis,[1] or pulmonary consumption, is, unfortunately, one of the commonest of diseases, the mortality from it being 1·2 per 1000 living (in 1903). The disease is caused by invasion of the lung by the tubercle bacillus, but the mode of such invasion is disputed. Koch is probably right in ascribing the infection to air-borne bacilli derived from the dried and powdered expectoration of phthisical persons, and hence the supreme importance of insisting on the disinfection of the sputum and the suppression of the filthy habit of spitting. Behring, however, asserts[1] that milk containing tubercle bacilli and used for the feeding of infants is the chief cause of consumption. He believes that the bacilli so ingested are absorbed and become deposited in the various lymphatic glands, in which they may lie dormant for a considerable time, afterwards becoming disseminated. Certain cases of pulmonary tuberculosis are hæmatogenous—*i. e.* the bacilli are carried by the blood-stream from other tuberculous foci. The hereditary transmission of tubercle bacilli from mother to offspring is probably of extremely rare occurrence, but an hereditary tendency to tuberculosis is common, and not infrequently whole families are wiped out by this scourge. The disease is particularly one of young adults, but no age is exempt, and a senile form is not infrequent. Some races are more susceptible than others.

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[1] The term "phthisis," though now usually restricted to tuberculous pulmonary disease, was formerly applied to any wasting disease; hence such expressions as *phthisis pulmonum*, renal phthisis, laryngeal phthisis, etc.

Pathologically, three varieties of pulmonary tuberculosis may be distinguished.

PNEUMONIC TUBERCULOSIS, or tuberculous pneumonia, is one of the commonest forms. It probably arises by inhalation of tubercle bacilli, which become arrested on the mucous membrane of the bronchioles or air-cells. Three stages are usually described :

(1) *Catarrhal stage.*—A catarrhal inflammation of the air-cells occurs; the walls of the alveoli become infiltrated with round cells and their cavities filled with catarrhal and round cells; the process extends to neighbouring air-cells until a small nodule or miliary tubercle is formed in which giant-cells are present.

(2) *Stage of caseation.*—With the progressive increase in size the central portion of the nodule tends to lose its vitality, coagulative necrosis follows, the cellular structure becomes completely obscured, and caseation ensues. The nodule at the same time may grow at the

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[1] *The Suppression of Tuberculosis*, Wiley & Sons, 1904.

periphery or form secondary nodules, so that considerable areas may be involved, a zone of catarrhal pneumonia always surrounding them.

(3) *Stage of excavation.*—By the softening, disintegration, and expectoration of the caseous material excavation ensues and a cavity is formed. Frequently several small cavities first appear and subsequently coalesce, forming one large cavity or *vomica.* The cavities contain more or less yellowish purulent fluid, usually free from fetor, with curdy masses and remains of lung-tissue. Their shape is irregular or sometimes rounded, their walls are rough and nodular, fibrous bands may cross them, a large bronchus frequently opens into them, and the vessels may be eroded or present aneurysmal dilatations owing to loss of support—a potent source of hæmorrhage or hæmoptysis. Both lungs may be affected or sometimes first one and then the other. The apex of the lung is particularly the seat of election of the tuberculous process, from whence it may spread downwards and involve the whole lung, but any part of the lung may be primarily involved. The pleura usually becomes thickened and adherent during the second stage; it may become infected and the bronchi are generally involved. Although the disease has a marked tendency to progress, it sometimes becomes arrested, generally in the second stage, and cicatrisation and calcification lead to a cure. That the disease may become arrested in an initial stage seems to be proved by the frequency with which cicatrisation and calcification in the apex are met with post mortem (in some 5 per cent. of all cases not presenting any other sign of tuberculosis).

The sputum, as already remarked, is usually free from fetor, and in the stage of excavation is voided in masses (nummular) of a yellowish or greenish colour consisting of muco-pus, and containing a variable number of tubercle bacilli and fragments of lung, particularly elastic tissue, and frequently blood. The disease may spread to other parts, frequently to the larynx and intestine, and may become generalised. Lardaceous disease of the liver and kidney sometimes supervenes, and empyema is not infrequent.

HÆMATOGENOUS TUBERCULOSIS of the lung develops in consequence of the transportation of tubercle bacilli from some other focus by the circulation. It is more common in children than in adults, and may be a part of acute general tuberculosis. This usually results in the development of a number of scattered tubercles. The bacilli become arrested in the capillary vessels, and there set up changes resulting in endothelial and round-cell proliferation and the formation of small, rounded, miliary tubercles sharply defined from the surrounding pulmonary parenchyma, which, although they may occur in closely aggregated groups, are usually separate from one another; the tubercles later caseate and appear as little yellow nodules. Surrounding each tubercle is a zone of catarrhal pneumonia and interstitial infiltration.

In rare instances the infection seems to be propagated by the lymphatics.

FIBROID PHTHISIS, cirrhosis of the lung, is a form of the disease in which the process is very chronic, leading to considerable interstitial change and fibrosis. The tuberculous areas become encapsuled and contracted by fibrous hyperplasia, and bronchiectasis is frequent. It is usually seen in those who have passed 30 or 35 years of age.

PULMONARY SYPHILIS is regarded as very rare, though it can hardly be doubted that some forms of interstitial fibrosis occurring in connexion with chronic bronchitis may have this origin. Gummata are extremely rare. An interstitial fibroid pneumonia beginning at the root of the lung has been ascribed to syphilis. *White pneumonia of the fetus*, a hyperplasia of the interalveolar connective tissue, and resulting in consolidation, occurs in syphilitic fetuses.

PULMONARY ACTINOMYCOSIS may be primary, or secondary to oral or pharyngeal, etc., actinomycosis. Clinically and in its results it closely resembles pneumonic tuberculosis. The yellowish actinomycotic granules may be met with in the expectoration or in the pus of the empyema which frequently occurs. *Pulmonary aspergillosis* may occur. *Glanders* of the lung is very rare.

TUMOURS.—Primary tumours of the lung are very rare. Round-celled *sarcoma* may occur, also *endothelioma* of the pleura, and *carcinoma*, starting from the bronchial mucous membrane. Secondary growths are not infrequent and are sometimes chondromata.

PARASITES.—Echinococcus cysts occasionally occur and may be primary or secondary to cysts in the liver. The contents may be expectorated and fragments of the cyst wall and hooklets be found in the sputum. Endemic hæmoptysis occurring among the Chinese and Japanese is caused by a fluke, the *Distomum Ringeri* or *Paragonimus Westermanii.*

The *Amœba coli* may also be expectorated if an amœbic liver abscess burst into the lung or pleural cavity.

The Pleura.

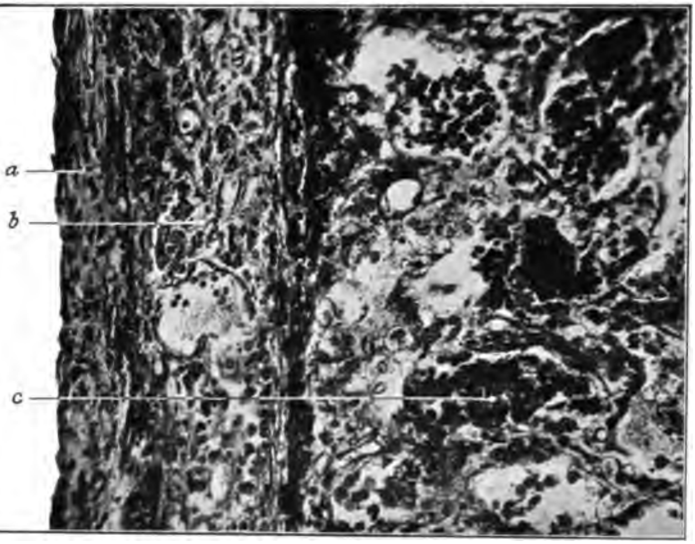
PLEURISY, pleuritis, or inflammation of the pleura, is very common. It may be secondary or primary. Secondary pleurisy accompanies any inflammatory process in the adjacent lung, chest-wall, or diaphragm, and thus may be met with in pneumonia, tuberculosis, peritonitis, hepatitis, thoracic wounds, caries of the ribs, neoplasms, etc.

Primary pleurisy may be infective and due to pyogenic cocci, the pneumococcus, tubercle bacillus, typhoid bacillus, etc., or may apparently be idiopathic, and occurs particularly in rheumatic individuals. Some would ascribe every apparent idiopathic pleurisy to the tubercle bacillus, and undoubtedly a considerable proportion of the cases are due to this cause. The pleurisy may be fibrinous or suppurative, the latter always being infective. The pleura becomes red and hyperæmic, it loses its glistening appearance, there is a subserous infiltration, and the capillary vessels are dilated and a fibrinous exudation (lymph) covers the inflamed area (Pl. XV., A.). More or less serous exudation occurs into the pleural cavity; in "dry" pleurisy it is small in amount. As the inflammation subsides the fluid is usually absorbed, and recovery may be almost complete, but frequently the fibrinous exudate becomes organised, giving rise to adhesions, and the pleura thickened. If the pleurisy be infective, the exudate, instead of being serous, is purulent, and the condition is known as *empyema*. In children half the cases of empyema are pneumococcic and 14 per cent. tuberculous, while in adults half the cases are streptococcal, 25 per cent. are tuberculous, and 17 per cent. pneumococcic. Empyema may also result from rupture of a phthisical cavity or of a neighbouring abscess—*e. g.* of the liver—into the pleura.

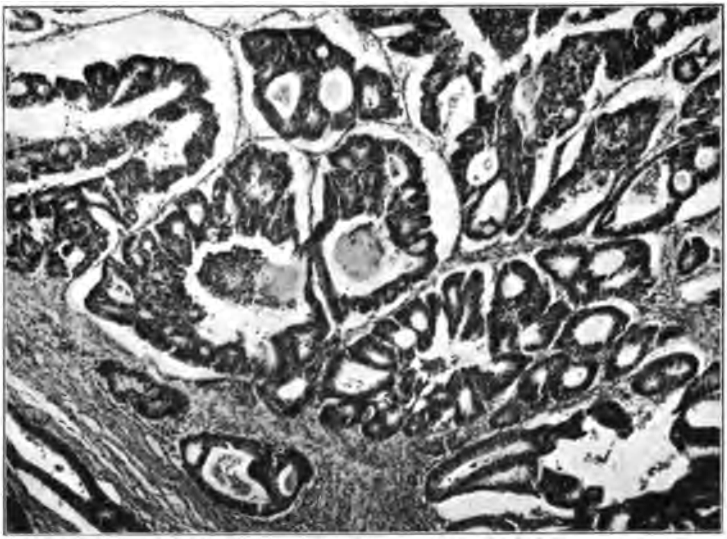
Hydrothorax, serous fluid in the pleural sac, may be due to inflammation, but occurs especially in chronic cardiac and renal diseases.

Pneumothorax, air or gas in the pleural sac, usually results from the rupture of a tuberculous cavity, rupture of an empyema into a bronchus, or from a perforating wound—*e. g.* from a fractured rib. It may rarely occur in a healthy lung from violent straining efforts. Pneumothorax is usually accompanied by serous exudation (hydro-pneumothorax) or pus-formation (pyo-pneumothorax). If the pus of an empyema becomes infected with putrefactive organisms, decomposition may ensue, with the formation of gaseous products, usually of an offensive character. In aseptic wounds of the lung, as from simple fractured rib, the air escaping into the pleura has been deprived of its organisms by filtration through the air-passages, as was first

PLATE XV.



A. Acute pleurisy. *a*. Layer of lymph. *b*. Thickened pleura with dilated vessels and inflammatory cells. *c*. Adjacent lung in a condition of catarrhal pneumonia. (Hæmatoxylin and eosin, × 40.)



B. Colloid carcinoma of the colon. (Hæmatoxylin and orange rubin, × 65.)

To face page 320.

pointed out by Lister, and little harm usually results. In perforating wounds from the outside there is the risk of sepsis. The effect of air in the pleura is to cause great dyspnœa, with collapse of the lung, general or local, since the ordinary negative pressure within the pleural cavity becomes atmospheric or even positive. In the case of tuberculous cavities the perforation is frequently surrounded by adhesions, which limit the extent of pleural cavity involved and the amount of collapse of the lung. In some instances, in consequence of a valvular opening admitting air during inspiration but preventing its exit during expiration, the intra-pleural pressure may become positive. Double pneumothorax (complete) is incompatible with life. Supposing that the perforation into the pleura closes, which is the rule in perforating wounds, but the exception in tuberculosis, the air is gradually absorbed, the intra-pleural pressure becomes negative once more, and recovery may be complete, though if the collapse has existed for some time, complete re-inflation may not be possible.

Fluid is removed from the pleural sac by absorption, chiefly by the lymphatics, to some extent also by the blood-vessels. A large effusion is removed relatively more slowly than a small one, since the area of the absorbing surface varies only as the *square* of the diameter of the cavity, while the volume of the effused fluid varies as the *cube* of the diameter. A pleural effusion renders the respiration quicker and shallower owing to pressure on the affected lung and on the heart. On the unaffected side the respiratory movements are increased and the lung undergoes compensatory over-distension. The pain in pleurisy is frequently referred to the abdomen.

TUBERCULOSIS of the pleura is usually secondary to pulmonary tuberculosis, but occasionally to tuberculosis of the ribs, bronchial glands, etc. Primary tuberculosis is the exception in man, but common in cattle, producing the *perlsucht*, or pearl disease. Tubercles form on and in the pleura, and set up around a fibrinous pleurisy, tending to produce thickening and adhesions.

Primary *tumours* and *parasites* are rare; secondary tumours may involve the pleura by direct extension or by metastasis. *Endothelioma* is a rare primary malignant growth, characterised by the formation of cell-nests of epithelial-like cells imbedded in a dense fibrous stroma.

The *mediastinum* is not often the site of primary pathological conditions. Inflammation may extend from the pleura and cause mediastinal abscess, and tuberculous lymphatic glands are not infrequent. A primary inflammation of the mediastinal areolar tissue, mediastinitis, has been described. Tumours may occur, carcinoma being usually secondary, sarcoma sometimes primary.

CHAPTER XV.

DISEASES OF THE DIGESTIVE SYSTEM—DISEASES OF THE LIVER—DISEASES OF THE PANCREAS.

THE DIGESTIVE SYSTEM.

For descriptive purposes, the mouth, pharynx, and accessory structures, the salivary glands, the œsophagus, stomach, intestine, omentum and peritoneum, and the liver and the pancreas will be included under the digestive system.

There is no need to give a detailed description of the histology and functions of the various organs and structures, but before considering each part of the digestive apparatus in detail it will be convenient to discuss certain general features and symptoms connected with it.

Disorders of secretion.—The *salivary secretion* is diminished in fevers, in diseases in which there is an excessive discharge of fluid elsewhere, such as diabetes and diarrhœa, by some drugs—*e. g.* belladonna, and in certain cases of neurosis—*e. g.* fright. This is not of particular importance, except as interfering with mastication, deglutition, and speaking. The salivary secretion is increased (*ptyalism*) in connexion with tumours in the region of the medulla, in bulbar paralysis, and by some drugs—*e. g.* mercury and the iodides. In bulbar paralysis the excessive secretion of saliva is partly apparent on account of the difficulty of swallowing, but not wholly so. Mercury probably acts reflexly by the concurrent stomatitis, the iodides by being secreted selectively by the saliva. Reflex ptyalism also sometimes occurs in pregnancy, gastric ulcer, neuralgia, etc.

The *gastric secretion* is chiefly disordered with regard to the amount of hydrochloric acid formed. This constituent may be diminished (*hypoacidity* or *achlorhydria*) in atrophy of the mucosa, chronic catarrh, cachexia, anæmia, in neurosis, and particularly in carcinoma. Not only does this occur in carcinoma of the stomach, but also in carcinoma in distant parts, as recently shown by Moore.[1] The deficiency of acid not only interferes with digestion, but allows micro-organisms to flourish, and hence decomposition of the gastric contents ensues, with the production of gases, acetic, lactic, and butyric acids, etc. The amount of pepsin is also diminished in some forms of dyspepsia, cachexia, carcinoma, etc. Hypersecretion of gastric juice occurs in certain nervous affections—*e. g.* hysteria and tabes, and hyperacidity may be present in gastric ulcer, excessive use of tobacco, etc.

Vomiting may be dependent on gastric causes—*e. g.* inflammation, dilatation, ulcer, cancer, indigestible food, etc., or may be of nervous origin, and occurs in hysteria, pregnancy, tabes (the gastric crises), migraine, and neuralgia, and especially in cerebral tumour. Pain and shock may induce nausea and vomiting, also events acting psychically—*e. g.* unpleasant sights or odours. The nervous causes may in some instances partly act through disordered secretion, as in pregnancy.

Fæcal vomiting, the vomiting of the intestinal contents, occurs in, and is an important sign of, intestinal obstruction. It is brought about probably, not by reversal of peristalsis, as used to be taught, but by a reversal of the axial stream of the intestinal contents. Peristalsis mainly acts on the contents of the bowel in contact with its wall, and since there is obstruction and the contents cannot pass onwards, they return along the line of least resistance, viz. in an axial stream.

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[1] Royal Society, March 16th, 1905.

DIARRHŒA is a symptom of many diseases. It may depend on (*a*) excessive excretion of fluid into the bowel, (*b*) diminished absorption of fluid from the bowel, (*c*) increased peristalsis, (*d*) defects in nervous control, and there is often more or less combination of two or three of these factors. Catarrh increases excretion, diminishes absorption, and promotes peristalsis; croton oil and irritant poisons promote peristalsis; magnesium sulphate causes a copious excretion; mental states (*e. g.* the stress of examinations, fright, etc.) probably increase peristalsis. The spurious diarrhœa which may appear in the later stages of obstruction is due to failure of absorption.

DISORDERS OF ABSORPTION may occur, and substances which should be absorbed are passed. This is chiefly the case as regards fat, the absorption of which is much diminished in pancreatic disease, but may also affect proteids and carbohydrates.

RETENTION OF FÆCES may be relative (constipation) or absolute (intestinal obstruction).

Constipation may result from (*a*) obstruction from pressure on the bowel (*e. g.* by tumours), from adhesion and cicatrices, and from disease of the intestinal walls—*e. g.* cancer; (*b*) impairment of propulsive power, either of the intestine or of the accessory muscles of defæcation, the abdominal muscles and diaphragm, as in lax abdominal walls from successive pregnancies, etc.; (*c*) abnormal dryness and hardness of the fæces, from altered relation of absorption and excretion, deficient intake of fluid, etc.; (*d*) lowering of the reflex irritability of the centre for defæcation in the lumbar cord. This is seen in myelitis, tabes, etc. Habit has, of course, a considerable influence in the genesis of simple constipation, and there is great variation in the frequency of defæcation. Some individuals seem to get on perfectly well with a weekly or less frequent evacuation!

Absolute retention of fæces occurs only in intestinal obstruction and acute peritonitis. Sudden obstruction with retention is usually fatal within five or six days, but absolute retention of *gradual* onset may last for a long period—weeks, or even months—the patient being troubled merely with severe dyspeptic symptoms. The cause of the difference in the two cases is difficult to explain; it may depend on the shock and peritonitis which usually accompany acute obstruction but are generally absent in the chronic form.

The Mouth, Tongue, and Accessory Structures.

MALFORMATIONS due to abnormal development are common, particularly *cleft* or *hare lip* and *cleft palate.* These are either unilateral or bilateral; in the latter they often appear to be mesial. In development a palatine process on either side grows inwards from the maxilla, and the ethmo-vomerine septum grows downwards, and the three should meet and unite about the ninth or tenth week. If this does not occur, the defects mentioned result, their extent and arrangement depending on the state of growth of the three constituents. These malformations are of importance only as regards feeding and speaking. The uvula may also be bifid. Other defects, such as absence or smallness of the maxillæ, occur.

Anæmia or *hyperæmia* of the mucous membrane occurs in anæmia, in inflammation, and in chronic cardiac and pulmonary diseases.

STOMATITIS, inflammation of the buccal mucous membrane, is of various kinds. In *catarrhal stomatitis* the mucous membrane is first reddened and swollen; there is to begin with excess of secretion containing a few leucocytes and desquamated cells, but as these increase dryness supervenes, and a pasty coating or "fur" covers the affected parts. It is met with after exposure to heat and cold, mild irritants, and in infective diseases. *Aphthous stomatitis* is a peculiar form of catarrhal inflammation, characterised by the appearance of whitish patches 1–3 mm. in diameter, termed "aphthæ." These seem to consist of a solid fibrinous exudation under the epithelium. It is common in badly nourished children, in cachexia, and during pregnancy.

Ulcerative stomatitis is an acute affection generally commencing at the alveolar margins of the gums. The tissue first becomes swollen and infiltrated and then undergoes necrosis, forming an ulcer, which may deepen and extend to the alveolar process. It generally attacks badly nourished children, but poisons such as mercury may be a cause.

Cancrum oris, noma, or gangrenous stomatitis, usually attacks one cheek and may commence as an ulcer or may occur independently. The tissues rapidly necrose and break down into a putrid gangrenous mass, and the process may extend right through the cheek. Once started it spreads with great rapidity and may involve the whole of one side of the face. The process is certainly an infective one, and diphtheria-like bacilli have been isolated. The disease usually occurs in badly nourished children.

Suppurative inflammation most commonly attacks the alveolar border (gum-boil) in connexion with carious teeth, and the tongue (glossitis) in connexion with wounds.

Thrush is a parasitic affection of the mucous membrane of the tongue and cheek due to the *Oidium albicans,* which grows mainly in the middle layers of the stratified epithelium, so that the superficial layers are raised and shed. Small white patches appear, which may coalesce and form almost a membrane. When removed, the mucous membrane beneath is reddened or may be superficially ulcerated. It attacks infants the subjects of imperfect feeding and malnutrition, and adults in the course of wasting diseases, often shortly before death.

GLOSSITIS, inflammation of the tongue, may be *catarrhal,* and accompanies and resembles catarrhal stomatitis (see above), or *acute parenchymatous,* occasionally arising from wounds, bites of insects, etc., but generally from the injudicious use of mercury. In the latter the tongue becomes enormously swollen and œdematous, so as to fill the mouth or protrude from it, and thus may interfere with deglutition and respiration, and if the condition spreads, œdema of the glottis may follow. There is considerable fever and suppuration often ensues.

Chronic superficial glossitis is a condition of considerable importance, since in nearly one third of the cases it terminates in carcinoma (Barker). It is usually a tertiary syphilide, to which has been added the irritative effects of alcoholism, excessive smoking, ragged teeth, chronic dyspepsia, etc. At first the papillæ become enlarged, swollen, and hyperæmic. Overgrowth of epithelium then follows, forming thickened whitish patches (*leucoplakia*). Next the excess of epithelium is shed, leaving smooth red patches in which the papillæ are atrophied, and if extensive forms the *glazed red tongue* so characteristic of tertiary syphilis. Lastly, cracks, fissures, and ulcers develop. It is very intractable to treatment.

Tuberculosis is rare and chiefly affects the tongue.

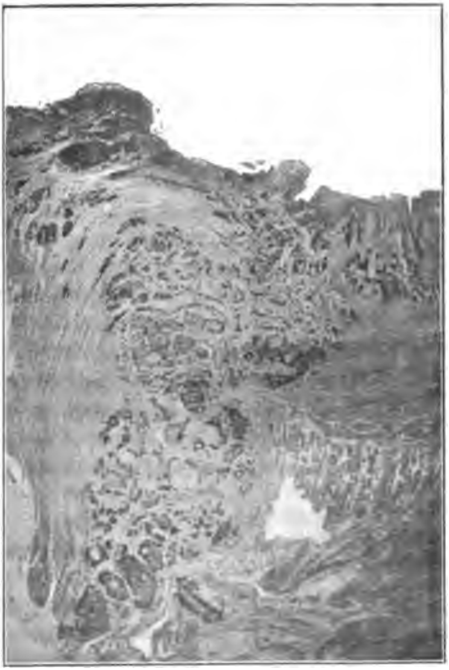

Fig. 10.—Section through carcinomatous tongue and subjacent tissue showing infiltration of the geniohyoglossus, etc. × 4.

It is generally secondary to pulmonary or laryngeal tuberculosis, occasionally primary.

Syphilis has been mentioned in connexion with glossitis which is usually tertiary, but the primary sore may develop about the lips or face, and secondary affections in the form of condylomata and mucous patches occur on the lips and tongue.

ACTINOMYCOSIS has one of its most frequent seats in the tongue and jaws. In the latter situation it may at first simulate a periosteal sarcoma.

HYPERPLASIA may be congenital or infantile and affects the lips (*macrocheilia*) and tongue (*macroglossia*). It is usually due to fibrous hyperplasia and dilatation of the lymphatics. Shattock[1] has described a case of macroglossia due to a fibromatosis of the nerves. *Atrophy* of the gums and alveolar parts of the jaws follows loss of the teeth.

CARCINOMA of the squamous type has one of its most frequent sites in the lips and tongue, and often starts from some point of irritation, ragged teeth, etc.; it is less frequent in other parts of the mouth. First nodular, it soon ulcerates and spreads by contiguity along the muscular bundles connected with the part—*e.g.* from the tongue along the hyoglossus, geniohyoglossus, etc. (Fig. 10), and to the lymphatic glands in the neck and under the chin.

SARCOMA mainly affects the jaw or gums and is not infrequent. In the jaw it is generally of the myeloid type, in the gums spindle-celled. It may start in the periosteum or in the bone-marrow.

EPULIS is the name given to any tumour of the gums close to the teeth. It may be a fibroma or a spindle-celled sarcoma (malignant epulis).

ANGEIOMATA may occur, chiefly on the lips, and *lymphangeiomata* also; the latter may form small cystic growths (cystic hygroma). *Papillomata* are not infrequent on the tongue.

The Teeth.

Caries of the teeth arises first in some small chips or deficiency in the enamel. This allows the lodgment of bacteria, particularly acid-producing forms, with gradual decalcification, erosion, and excavation of the dentine. The pulp or periosteum may finally become affected and the tooth be reduced to a mere shell of enamel.

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[1] *Path. Soc. Trans.*, vol. liv, 1903, p. 243.

Pyorrhœa alveolaris, Riggs' disease, is a chronic intractable suppurative condition of the margins of the gums and sockets of the teeth. Goadby has isolated a staphylococcus which differs somewhat from *S. pyogenes aureus.*

Inflammation of the pulp and periosteum may pass on into suppuration, forming an alveolar abscess or a gum-boil, or occasionally may spread widely and cause necrosis of the jaw, etc.

Tumours of the teeth are not common. *Dental osteoma* is practically an inflammatory hyperplasia of the cement substance. *Odontoma* is a neoplasm arising from the pulp in the early stages of growth, and consists of dentine and enamel. *Dentigerous cysts* are cysts of the jaws produced by dilatation of the dental follicles. They may be of large size and contain a fluid in which rudimentary teeth are occasionally found.

Congenital syphilis occasions the well-known and characteristic "Hutchinson's teeth." The upper central incisors are peg-shaped, short, and thin, smaller at the base than at the crown, notched at the centre of the crown, and frequently yellowish.

Tartar is a deposit of organic salts of calcium on the teeth.

The Salivary Glands and Neck.

Epidemic parotitis, mumps, is an infective disease affecting the parotid glands, which become much swollen and tender. The other salivary glands may be slightly involved. After lasting for a few days, and accompanied by some fever, resolution takes place, suppuration never occurring. It is frequently complicated by a simple orchitis or oophoritis. The micro-organism is unknown. Other infective diseases—*e.g.* typhoid, variola, diphtheria, etc.—may involve the salivary glands and sometimes cause suppuration.

Angina Ludovici, Ludwig's angina, is an acute phlegmonous inflammation of the tissues around the submaxillary gland and under the deep cervical fascia, and may originate from middle-ear disease, the infection travelling *viâ* the digastric muscle. It causes considerable brawny swelling under the jaw and in the neck, with dyspnœa, and ends in suppuration or gangrene, sometimes in pyæmia.

Salivary fistula results from inflammation or wound of a salivary duct.

Occlusion of a salivary duct causes dilatation from the retained secretion. The cysts produced by obstruction of the submaxillary and sublingual ducts project beneath the tongue and are known as *ranulæ*.

Salivary calculi consist of calcium carbonate and phosphate, and occasionally occur in Wharton's and Stenson's ducts.

Tumours of the salivary glands may be adenomata, fibromata, chondromata, sarcomata, or carcinomata. A peculiar form of tumour occurs in the parotid, the "parotid tumour," and occasionally in the other salivary glands and in the palate, and has been variously described as a chondroma, myxoma, sarcoma, etc., according to the type of tissue predominating, but is now regarded as an endothelioma. This tumour consists[1] of a stroma, generally of a myxomatous type, often intermixed with fibrous tissue, which in places may be hyaline and with the enclosed cells resemble cartilage. Cartilage may also be present. The cells are usually small, spheroidal or polyhedral, and arranged in strands or columns, in some cases appearing like tubular or circular gland acini. The cells in places are abundant and with the merest strands of connective tissue passing between them. The true cartilage in this, and in the enchondromata which are met with in the salivary glands, arises from inclusions of Meckel's cartilage of a branchial arch. The parotid tumours are not usually malignant, but tend to recur *in situ* unless completely removed.

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[1] See Johnson and Lawrence, *Path. Soc. Trans.*, vol. liv, 1903, p. 329.

The *potato tumour* of the neck, described by Jonathan Hutchinson, grows from beneath the sterno-mastoid and appears to originate from the carotid body or gland at the bifurcation of the common carotid; this body is of mesoblastic origin, and the tumour, therefore, is an endothelioma.[1] The growth consists of a delicate embryonic connective-tissue stroma enclosing alveoli containing rounded or oval cells. Other growths (the *branchiomata* of Volkmann), some purely epithelial, others mixed epithelial and endothelial, arise from remnants of the branchial arches and may develop under the chin or below the parotid.

Various malformations arise in connexion with the branchial arches. In man there are four post-oral arches, the fourth and fifth being amalgamated, each consisting of mesoblast lined on either side by epiblast; between them are the branchial clefts. If the latter do not close properly, branchial fistulæ result (see also p. 300), or if imperfectly closed, branchial cysts. Cysts may also occur in connexion with the thyro-glossal duct (cystic hygroma). The thyroid is considered elsewhere.

Torticollis, or wry neck, is a condition produced by contraction of the sterno-mastoid. It may be congenital, due to some uterine malposition, etc., or may result from spasm due to irritation in the neighbourhood—*e.g.* glands or cervical caries, hysteria,—or be paralytic.

Enlarged glands, either tuberculous, or of Hodgkin's disease, or secondary to malignant disease, are common in the neck.

A curious condition has been described by Lannois and Bensaude. It consists of soft swellings about the nape of the neck and the back, corresponding to certain lymphatic areas, in which lymphoid tissue is present, and has been termed "adenolipomatosis."

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[1] See Gilford and Davis, *The Practitioner,* December, 1904, p. 729.

The Palate, Pharynx, and Tonsils.

The mucous membrane of these parts of the oral cavity is characterised by its richness in lymphoid tissue. Inflammation of the throat is referred to generally as "angina."

Pharyngitis may be acute or chronic. The chronic form frequently results from chronic irritation, smoking, irritant particles and vapours, etc. Small granular masses of lymphoid tissue are often present (granular pharyngitis). Catarrhal and follicular pharyngitis also occurs.

Hyperplasia of the tonsils is a common affection in children, and is often associated with adenoids. The enlargement is of importance as interfering with respiration, etc. The cause is unknown.

Adenoid vegetations are lymphoid nodules in the pharynx and posterior nares. They often completely block the posterior nares, and their presence is conducive to many evils—mouth-breathing with accompanying catarrh, mal-development of the lower jaw and projection of the upper teeth, mental dulness, etc. The cause is unknown.

Retropharyngeal abscess is generally due to cervical caries.

Tonsillitis may be catarrhal, follicular, or parenchymatous (*quinsy*), and may terminate in suppuration. It seems particularly to be associated with the rheumatic diathesis.

One of the most important forms of inflammation in the throat is the *diphtheritic*. Hyperæmia with swelling first occurs, and then the formation of greyish spots or areas, which may coalesce to form extensive patches of the yellowish wash-leather membrane. If the membrane be removed it leaves a bleeding surface.

The epithelium is infiltrated and undergoes coagulative necrosis, and a fibrinous exudation covers the surface. The membrane may extend over the palate, up the posterior nares to the nose, and downwards into the larynx, trachea, and even into the bronchi, and rarely into the œsophagus and stomach.

Tuberculosis only occasionally affects the tonsils, palate, etc.

Syphilis is common, particularly in the secondary stage as mucous plaques, occasionally in the tertiary as a gummatous infiltration. Ulceration of the palate, frequently going on to perforation, is commonly syphilitic.

Malignant disease, sarcoma and squamous-celled carcinoma, is not infrequent (it should be remembered that cell-nests may occur in the normal tonsil). *Simple adenoma* of the mucous glands occurs.

The Œsophagus.

Malformations. — Congenital stenosis may occur. Sometimes there is a fistulous connection with the trachea, or a bronchus.

Inflammation may be produced by hot liquids or chemical irritants.

Stricture is due to contraction of cicatrices after inflammation, especially that produced by chemical irritants, rarely to syphilis, frequently to malignant disease, occasionally to pressure from without—*e. g.* aneurysm. *Spasmodic* stenosis occurs in hysterical patients.

Dysphagia, difficulty or pain in swallowing, may be due to stricture and its causes, and occurs also in bulbar paralysis.

Diverticula arise either from pressure from within acting on a weakened muscular wall, or traction from without—*e. g.* adhesion of caseous glands.

Rupture is rare, and is almost always secondary to disease of the wall.

Various tumours have been met with in the œsophagus, but by far the commonest and most important is carcinoma of the squamous-celled type, which occurs usually in the lower third. It may be nodular or annular, gives rise to dysphagia and stricture, frequently ulcerates, and may cause perforation.

Thoracic aneurysm may ulcerate and rupture into the œsophagus. A bougie should never be passed in œsophageal stenosis until this cause has been excluded, or rupture may be produced.

The Stomach.

Malformations.—The stomach is occasionally absent in acephalic monsters. It may be transposed with the other viscera, and is occasionally constricted at the middle, giving an hour-glass shape, and apparently due to persistence of a physiological state of contraction.

Hour-glass contraction or deformity may also be due to cicatrisation of an ulcer, tumours, torsion, etc.

Congenital hypertrophic stenosis of the pylorus.—This affection occurs exclusively in infants a few weeks old, but the condition has also been supposed to account for gastric symptoms in later life. Vomiting is the prominent symptom. Post mortem, an overgrowth of the circular muscular fibres of the pyloric segment of the stomach is present, most marked in the position of the pyloric sphincter. Three theories have been advanced to account for the condition: (1) That the contraction is spasmodic and the result of irritation, and arises after birth, the muscular hypertrophy being secondary; (2) that the condition is a developmental hyperplasia of the pyloric muscles; (3) that the hypertrophy is secondary to spasm arising from disturbances in nervous co-ordination. The last seems to be the theory which has the most to support it.[1]

Dislocation of the stomach may take place through defects in the abdominal wall, diaphragm, etc. *Gastroptosis* (Glénard's disease) is a condition in which the gastro-hepatic and other "ligaments" are relaxed so that the pyloric orifice descends and the viscus assumes a more vertical position. It is frequently associated with prolapse of other viscera, especially the transverse colon, liver, and right kidney (enteroptosis). Glénard has suggested that this state of affairs is the basis of neurasthenia. The causes are tight lacing, pregnancy, abdominal tumours, etc.

Dilatation of the stomach may result from stenosis of the pylorus, due either to cicatricial contraction or usually to cancer, from habitual overloading with indigestible food as in navvies, from atony as in the course of long-continued fever, and from habitual dyspepsia, especially flatulent. In certain cases *acute dilatation* takes place from rapid ingestion of quantities of food or drink, or other causes not defined. The maximum capacity of the normal stomach probably never exceeds 1600 c.c.

Gastric tetany.—Tetany is most frequently met with in association with gastric disorder, particularly dilatation. Albuminuria has frequently been noticed during the attacks; in some cases chronic nephritis has been found post mortem, and pylorectomy or gastro-enterostomy is stated immediately to relieve the symptoms and to prevent a recurrence of the spasmodic attacks. In some cases of tetany the thyroid is diseased, and tetany may occur in animals after removal of the thyroid. In one case of gastric tetany Halliburton[2] extracted a toxic substance from the gastric contents which produced marked fall of blood-pressure, and he regards the condition as an auto-intoxication, but generally no toxic substance has been found. Von Mering believes that the stomach produces an internal secretion which, if absent, leaves certain poisons unneutralised, and these produce toxic effects. Others have supposed that the vomiting which precedes the attack depletes the body of water and of chlorine.

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[1] See Clogg, *The Practitioner*, November, 1904, p. 624.

[2] *Brit. Med. Journ.*, 1901, vol. i, p. 1607. See also Moorhead, *The Practitioner*, August, 1904, p. 160.

Dyspepsia is a somewhat indefinite term used to indicate a disturbance of the digestive process in the stomach without gross anatomical lesion. Sometimes the mucosa is atrophic, frequently catarrhal ; occasionally ulceration is present, often dilatation. *Acid dyspepsia* is a frequent form, the patient suffering from acid eructations and burning pain in the epigastrium. Usually lactic acid is most abundant, with traces of butyric and acetic; occasionally the hydrochloric is in excess (hyperchlorhydria). In other cases there may be inability to digest proteid in the form of meat, etc., and in these probably the pepsin is deficient. Flatulent dyspepsia is the result of decomposition, particularly of carbohydrates, by micro-organisms. It is frequently associated with dilated stomach, and the presence of sarcinæ (which, however, are not the cause of the fermentation). Heartburn (pyrosis) is a frequent symptom in dyspepsia, a burning sensation in the epigastrium, and waterbrash is another, the eructation of a mouthful of watery acid fluid.

Hæmorrhage into the stomach wall occurs in leukæmia and pernicious anæmia, in acute yellow atrophy of the liver, scurvy, and purpura, in many acute infective diseases, and with poisons, such as phosphorus. Hæmorrhage into the stomach cavity occurs in these conditions, and in ulcer, simple or cancerous. Blood may, of course, be swallowed.

Gastritis, inflammation of the stomach, is in the majority of instances catarrhal. The surface is covered with a coating of mucus, shed epithelium, and leucocytes, the glandular epithelium is mucoid and desquamating, and the vessels of the inter- and sub-glandular tissues are dilated. The mucosa may be very red. It is caused by mild irritants, indigestible articles of food, etc. In the chronic forms the mucosa becomes atrophic and pale. Stronger irritants, such as acids, arsenic, etc., may cause a more intense form of inflammation, with considerable infiltration and redness, ulceration, and necrosis. Strong acids and the like produce necrosis before there is time for any inflammatory reaction, and the mucosa is greyish or yellowish, dry or pulpy, according to the irritant swallowed.

Phlegmonous gastritis is an intense form of acute gastritis occurring in the course of fevers, etc., and may end in abscess.

Membranous gastritis occasionally occurs in children, and is associated with septic infections and fevers. A true *diphtheritic* membranous gastritis is rare, and is due to extension from the pharynx.

Gastric ulcer, simple ulcer, is a common affection of young anæmic women, but less frequent in men. It consists in a rapid localised destruction of the mucosa and submucosa, or sometimes of all the coats, with consequent perforation. It is single or multiple, and has its most frequent seat on the posterior wall (45 per cent.) or on the lesser curvature near the pyloric end (25 per cent.). The edges of the ulcer, which is nearly circular, are well defined, as though punched out, and funnel-shaped, the wide orifice being at the mucosa. The size of the ulcer varies from 0·5 to 6 or 7 cm., but if perforation occurs the hole is generally quite small—not larger than a goose-quill. A patch of fibrinous lymph usually forms on the serous surface opposite the ulcer, which is thus often attached to neighbouring structures, and so perforation is prevented, or if this event happen extravasation is limited. The ulcer in course of time heals, becoming permanently attached to a neighbouring viscus, usually the liver, and its base covered with cicatricial tissue, but it is questionable whether the epithelium is regenerated over the area. In persons past middle life the ulcer is often very chronic and intractable. Besides perforation, the presence of the ulcer causes discomfort and pain, dyspepsia, vomiting, and, if it erode a vessel, more or less serious hæmorrhage. The ætiology of the affection is not completely understood. Experimentally, embolism of the branches of the gastric arteries produces a condition precisely similar, necrosis follows the embolism, and the necrotic area is digested by the gastric juice, and so the ulcer is formed. Emboli, however, have not been satisfactorily demonstrated in the gastric ulcer, and no particular cause to induce embolism is usually present, though the ulcer may follow burns, and Robson and others suggest that oral sepsis is responsible for many cases. A very similar condition is not infrequent in the duodenum, particularly after burns.

Tuberculosis and *syphilis* are rare.

CARCINOMA is common, its usual seat being the pylorus and lesser curvature, occasionally the fundus and cardiac orifice. Scirrhous carcinoma is the usual type, is most frequent at the pylorus, and often tends to run a chronic course. Medullary, colloid, and adeno-carcinoma also occur, rarely squamous, which commences at the lower end of the œsophagus, and invades the cardiac end. In some instances the cancer, particularly colloid, tends to infiltrate the walls of the stomach, but the scirrhus of the pylorus generally forms a tumour and causes stenosis. *Sarcoma* is exceptional. *Parasites* are rare, and as a rule wander upwards from the bowel—*e. g.* the round worm. *Foreign bodies* are not infrequent, accidentally swallowed, or swallowed purposely by hysterical or insane patients. In the Museum of the Royal College of Surgeons is a large mass of bent pins swallowed by a patient. In animals hair-balls occur.

The Intestines.

The pathological lesions of the intestine bear a general resemblance to those of the stomach, but three peculiarities in the anatomical structure of the intestine differentiate it in some respects from the stomach, and have an important bearing on certain of the disease processes attacking it. These are (1) the looseness of its connexions, allowing considerable mobility; (2) the presence of villi and abundant lacteals and lymphatics; and (3) the presence of lymphoid nodules, Peyer's patches and solitary glands, which are almost absent from the stomach.

Malformations.—Absence, inversion, and the like are occasionally met with; also hernial protrusions through defects in the abdominal wall, diaphragm, etc. The most important defects are those involving the lower portion of the bowel and urogenital sinus. The upper part of the rectum is developed from the lowest portion of the primitive hind gut, which is in communication with the bladder, forming a common cavity or cloaca, the lower part is developed by an ingrowth of the epiblast, the proctodeum, and various defects result from imperfect development of these various parts. The ileum may open into the bladder, vagina, etc , the intestine and urethra into a common passage; the of some laxity of the tissues about the anus. It is frequent in children.

Œdema occurs in general venous engorgement, cirrhosis of the liver, and ascites. *Passive hyperæmia* occurs under the same circumstances. It is of most importance in causing dilatation of the hæmorrhoidal veins, and the condition known as *hæmorrhoids*, or *piles*. Sedentary habits, chronic constipation, and pregnancy, all play a part in their production.

Inflammation, enteritis, may be non-specific or specific; the latter includes typhoid, tuberculous disease, dysentery, and cholera.

Of non-specific inflammations a catarrhal inflammation or enteritis is frequent. The mucosa is reddened and covered with patches of tough tenacious mucus; from the colon a very large amount of mucus may be secreted. The epithelial cells may be more or less shed and the lymphoid follicles enlarged and sometimes ulcerated. In some forms of catarrh membranous casts are shed (membranous catarrh). Diphtheritic and croupous inflammations may occur, but are rare. Atrophy of the mucosa often results from catarrhal inflammation.

Acute perforating ulcer of the duodenum is not infrequent, is very liable to follow burns of the skin, and is completely analogous with the similar ulcer of the stomach. Sepsis is the probable cause, excretion of septic products with the bile probably accounting for this location of the ulcer.

Different names are applied to inflammation of different parts of the intestinal tract. *Duodenitis,* usually associated with inflammation of the stomach, and often leading to obstruction of the bile-ducts and catarrhal jaundice; *ileitis, typhlitis, perityphlitis,* and *paratyphlitis,* inflammations of the cæcum and surrounding parts, are commonly primary inflammations of the appendix (*appendicitis*); *colitis* is generally specific, especially dysenteric; and *proctitis,* inflammation of the rectum, arises from local irritation of retained fæces, foreign bodies, parasites, and occasionally is gonorrhœal. *Ischio-rectal abscess* may occur, *fistula in ano*, and *fissure of the anus* may complicate proctitis. The latter is generally produced by hard scybalous fæces tearing one of the valve-like tags left at the junction of rectum and proctodeum.

LARDACEOUS DISEASE of the intestine, particularly of the ileum, is frequent in association with lardaceous disease elsewhere, the blood-vessels of the villi being the chief seat of deposit.

APPENDICITIS.—The normal appendix is of a yellowish-pink colour, is quite soft and pliable, and no contents can be felt within it. It averages 8–9 cm. in length and 5–6 mm. in thickness, reaches its greatest development between the ages of 10 and 25, after which it tends to involute. Structurally, it resembles the cæcum, but contains more lymphoid tissue, and its opening into the cæcum is guarded by a fold of mucous membrane (*valve of Gerlach*). In the herbivora the appendix is largely developed, and in man is usually looked on as a vestigial structure. Berry, however, regards it as a specialised part of the alimentary canal represented in the vertebrate kingdom by a mass of lymphoid tissue (usually seven masses or follicles) situated most frequently at the cæcal apex. It is usually described as functionless, but on this view must fulfil some physiological use. Battle and Corner[1] suggest that when the partially digested food enters the cæcum there is a temporary delay in the onward passage of the intestinal contents, which is associated with the development of numbers of micro-organisms and their products, and that the presence of a large amount of lymphoid tissue in the terminal and most dependent part of the cæcum—*i.e.* the appendix—serves as a defensive mechanism against these. The fact that the lymphoid follicles progressively decrease in number after puberty does not, however, support this view. The appendix is sometimes small or absent and may present various abnormalities of position, etc.

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[1] *Surgery of Diseases of the Vermiform Appendix* (Constable, 1904).

Appendicitis, inflammation of the appendix, is most common at about 20 years of age, and the large majority of cases occur between the ages of 15 and 35; before 10 and after 40 it is comparatively rare. Its maximum incidence coincides with the maximum development of the lymphoid tissue, which, after the twentieth year, progressively decreases in amount (Berry and Lack). The cause of the disease is not clear; in the acute ulcerative and gangrenous cases concretions undoubtedly are frequently present. These consist, not of foreign bodies (cherry-stones, etc.), as used to be supposed, but of inspissated fæces impregnated with lime-salts; parasitic worms are occasionally met with. Once a concretion has formed in the appendix, there is always risk of its setting up inflammation, which is followed by infection. Very rarely a typhoid ulcer is the starting-point of the condition.[1]

The kind of infection is shown in the following table (Battle and Corner):

Micro-organism.	Acute appendicitis.	Chronic appendicitis.
Bacillus coli communis in pure culture	70 per cent.	90 per cent.
„ „ with staphylococci	15 „	6 „
„ „ „ streptococci	7 „	Very rare.
Staphylococci alone	4 „	1 per cent.
Streptococci „	Very rare	Very rare.
Other organisms or combinations	4 per cent.	3 per cent.

It is not improbable that in a still greater percentage of cases a mixture of organisms is present at first, the *Bacillus coli* subsequently crowding out the other forms. The *Proteus vulgaris, B. pyocyaneus,* and *B. aerogenes capsulatus* also occasionally occur.

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[1] See a case recorded by Stokes and Arnick, *Johns Hopkins Hosp. Bull.*, vol. xvi, 1905, p. 284 (bibliog.).

The inflammation may be acute or chronic, and if recovered from is frequently recurrent. It may be divided into a catarrhal, a necrotic or gangrenous, and an interstitial type. The catarrhal, acute or chronic, is the mildest form; there is retention of the contents of the appendix, with some swelling and erosion of the mucosa. In the necrotic or gangrenous form the mucous membrane suffers rapid destruction and necrosis and the muscular and serous coats are soon involved. In the inflammatory process the appendix first becomes œdematous and swollen, and the mesentery being short, it then tends to become bent or kinked, and in the bend an ulcer commonly forms. The necrosis may take place at a single point leading to ulceration and perforation, or the whole appendix may become gangrenous. In the former case a local peritonitis and abscess may result, in the latter the destruction may be so rapid that there is no time for adhesions to form and a general peritonitis ensues. This variety is frequently associated with the presence of concretions. Interstitial change accompanies more or less all forms of appendicitis, but in the chronic form (chronic from the first or resulting from an acute or subacute attack) there is frequently considerable infiltration with round cells and subsequent fibrosis, which causes chronic thickening and sometimes obliteration of the lumen.

Mild cases of catarrhal appendicitis recover, but there is generally some thickening and adhesion, which often leads to recurrent attacks. Adhesions frequently become extensive, forming bands which are prone to give rise to further trouble. If widespread adhesions form, the disease may spread through the walls and perforation or rupture occur. If the adhesions be sufficient, a local abscess is the result (*perityphlitic abscess*), but if not general peritonitis ensues. The abscess, if unopened, may rupture externally into the peritoneal cavity, or into some viscus. There is always more or less systemic intoxication and infection and metastatic abscesses may occur.

Specific Inflammations of the Intestine.

TYPHOID FEVER.—The stress of the infection in typhoid (p. 132) usually falls on the intestine, which is also the primary site of infection in the vast majority of cases. The principal seat of the lesions is the lower part of the ileum and at the ileo-cæcal valve. The mucosa is swollen and hyperæmic and in a condition of catarrhal inflammation, but the characteristic changes are seen in the Peyer's patches and solitary follicles. These are inflamed, cellular proliferation and infiltration are marked, and they become swollen and project above the surface of the mucosa. According to Mallory[1] the cellular infiltration is not a leucocytic one to any extent, but is chiefly due to proliferation of the endothelial cells of the fibrous meshwork of the lymphoid tissue and of the lymphatic and capillary vessels. Some of the endothelial cells become fused and form giant phagocytic cells; a few leucocytes are present, but not many. This proliferation, infiltration, and swelling of the Peyer's patches, etc., progresses for eight or ten days, when it reaches a maximum, and then necrosis and sloughing occur, leaving a characteristic ulcer. The ulcer of the Peyer's patch is usually oval, but may be roundish if the necrosis be partial, its long axis coincides with that of the bowel and the floor is smooth and composed of the muscularis; but if the necrosis be partial, shaggy tags or patches of the mucosa and submucosa may be present. The mucosa is undermined at the edges of the ulcer, so that the margin floats when placed in water. The serous coat, so long as perforation is absent, shows little change. Sometimes the necrosis proceeds farther, through the muscular and serous coats, and results in the dreaded perforation. The hole may be a simple point or may be a ragged opening 1 cm. in diameter. Fæcal matter may thus escape into the peritoneal cavity and set up acute peritonitis. Fortunately, adhesions occasionally form which may limit the mischief. The solitary follicles in the large intestine and occasionally in the upper part of the small intestine, and even in the stomach, undergo much the same kind of changes. If recovery takes place, the ulcers heal, but without cicatricial contraction; their sites usually remain as smooth, depressed patches. Should the ulcer erode a vessel, hæmorrhage, more or less extensive, ensues. The mesenteric glands are always enlarged and sometimes suppurate. Exceptionally no lesions are found in the intestine, or they may be microscopic, and escape notice unless carefully searched for.

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[1] *Journ. of Exper. Med.*, vol. iii, 1898, p. 611.

Paratyphoid fever is a condition clinically closely resembling typhoid fever but due to infection with some variety of the paratyphoid bacillus, an organism allied to the typhoid bacillus but belonging to the Gaertner group (see p. 133).[1] Ulceration of the intestine is the exception, and when it occurs is more like dysenteric ulceration; the Peyer's patches and solitary follicles are practically unaffected, and the mesenteric glands unaltered; the endothelial proliferation and phagocytosis described by Mallory in typhoid are also absent.[1]

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[1] See Hewlett, *The Practitioner,* January, 1904, p. 173.

DYSENTERY is a clinical term used to denote a train of symptoms associated with colitis and mucoid and bloody diarrhœa. It is dependent on various causes, and at least four varieties may be distinguished—(1) tropical, endemic, or amœbic; (2) epidemic or bacillary; (3) sporadic; and (4) pseudo-dysentery due to various parasites, etc. Clinically, catarrhal, ulcerative, diphtheritic, gangrenous, etc., forms are recognised.

The milder forms of dysentery are simply a catarrhal enteritis or colitis, but in the more severe cases ulceration of the colon (ulcerative colitis) is present. This may give rise to a pseudo-membranous deposit on the mucous membrane, due partly to a fibrinous, and particularly to a mucoid, exudation, with desquamated patches of the mucosa (diphtheritic dysentery); in the most severe forms the term "gangrenous" is quite applicable.

The *tropical* or *amœbic dysentery* occurs particularly in the East, and is caused by the *Amœba coli* (*Entamœba histolytica* of Schaudinn, p. 138). If the acute stage be passed, it is characterised by a tendency to chronicity and relapses and to the occurrence of the single liver abscess as a sequel (p. 363). The mucous membrane is œdematous, swollen, and hyperæmic, and becomes necrotic and sloughs away, leaving an ulcer with infiltrated undermined edges. The base of the ulcer is formed by the infiltrated *submucosa,* the essential cause of the ulceration being infiltration of the submucosa, which leads to necrosis of the mucosa (Flexner). Microscopically, there is little leucocytic infiltration, but much proliferation of connective-tissue cells. Amœbæ are found in the tissues at the base and edges of the ulcer; they are also abundant in the early bloody mucoid stools.

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[1] See Wills and Scott, *Journ. of Infectious Diseases,* vol. i, 1904, p. 72.

Epidemic or *bacillary dysentery* occurs in all parts of the world, particularly in Japan, and in times of war and famine. It is caused by the *Bacillus dysenteriæ* of Shiga and Kruse (p. 134). The mucous membrane is congested, swollen, and hæmorrhagic. According to Flexner,[1] the histological changes appear in the mucous membrane, submucosa, and muscularis, being most marked in the two former situations. Those of the mucous membrane consist of coagulative necrosis, with exudation of fibrin and polymorphonuclear cells. The fibrinous and cellular exudate may entirely replace the glandular layer, or here and there a gland may be preserved. The pseudo-membrane is a close-meshed network of fibrin enclosing the multinuclear, often fragmented, cells. The blood-vessels are to be distinguished, but a variable number of red blood-corpuscles are mingled with the exudate, and lie free upon the surface. The muscularis mucosa is not always distinguishable—indeed, it is frequently lost in the exudate. The submucosa is always much altered. From the changes found there, it is evident that to them is chiefly due the thickening of the gut. The part most affected is the layer next the muscularis mucosa. Here hæmorrhages of variable size are seen, while in the interstices of the tissues some fibrin appears. More marked, however, are cellular accumulations, which are present, not uniformly, but in irregular areas. The deeper layers of the submucosa show similar cellular infiltrations, although the amount is less striking. On the other hand, at these levels the quantity of fibrin is greatly increased, and hæmorrhages are numerous.

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[1] *Johns Hopkins Hosp. Bull.*, vol. xi, 1900, p. 231.

The character of the cellular exudate is quite uniform. Excluding the red blood-corpuscles, the new cells consist chiefly of plasma-cells. These are collected into foci, often about blood-vessels, veins and arteries, but sometimes they occur in small groups or singly. There can be no doubt that these are identical with Unna's plasma-cells; they show the reticulated nucleus, often placed excentrically, and the fine blue granulations of cell-cytoplasm with eosin and methylene-blue staining. As the deeper levels of the submucosa are reached, hæmorrhages and fibrin are abundant. The size of the foci of plasma-cells gradually diminishes; at the muscular border they have almost disappeared. Among the plasma-cells a variable number of eosinophilic cells may be distinguished.

In the submucosa infiltration, hæmorrhage, and fibrin-formation take place, also beneath an intact, or almost intact, mucous membrane. The nature of the cellular infiltration may be identical with that already described, but, in addition, accumulation of lymphoid cells may frequently be seen. These exist in the layer of the submucosa, immediately next the muscularis mucosæ, the deeper cells resembling plasma-cells. The blood-vessels of the submucosa may be patent and congested, the blood containing an excess of white elements; or they may show recent leucocytic and fibrinous thrombi. Hyaline degeneration of the vascular walls was not encountered. Large spaces in the submucosa may contain fibrinous clots; these are probably dilated and thrombosed lymphatic vessels. The muscular coat shows only hæmorrhages, which may be of large size, although they are usually smaller than in the submucosa. The peritoneal tunic is usually unaltered.

The ulcerative colitis or asylums dysentery seems to be due to the

Bacillus dysenteriæ,[1] also some 60–70 per cent. of the cases of epidemic diarrhœa (summer diarrhœa) of infants.[2]

Sporadic dysentery—*i.e.* an acute colitis—may probably be due to a variety of micro-organisms, such as the *Proteus vulgaris*, *B. pyocyaneus*, etc.

Pseudo-dysentery may be caused by such parasites as the bilharzia and the *Balantidium coli*.

CHOLERA, Asiatic or epidemic cholera, or true cholera.—In this disease, which is caused by the cholera vibrio or comma bacillus of Koch, the mucous membrane is more or less congested and pinkish, and the lymphoid follicles are congested and swollen. The mucosa frequently has a sodden, pulpy appearance, from exfoliation of the epithelium, and small ecchymoses may be present; the outer surface of the bowel has often a rosy-red, injected appearance. These changes are most marked at the lower end of the ileum. The bowel contains the characteristic rice-water material, occasionally blood. The stools are quite fluid and pale, and almost like water, in which float little ragged, whitish flakes, consisting of mucus with some epithelium, and containing multitudes of bacteria, and generally numbers of the comma bacillus. Owing to the similarity of the stools to the water in which rice has been boiled, the term "rice-water stools" is applied to them; they contain urea, a trace of proteid, are neutral or faintly alkaline when fresh, and often give a pink colour on the addition of strong sulphuric or hydrochloric acid owing to the presence of indol.

The *Spirillum choleræ Asiaticæ* occurs in the bowel as a small curved rod (vibrio), but under cultivation grows into spirillar filaments. It is motile, having a single flagellum at one end, non-sporing, and non-Gram-staining. It slowly liquefies gelatin, and cultivated in peptone water forms much indol, which may be detected

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[1] See Eyre, *Path. Soc. Trans.*, 1901.

[2] See Hewlett, *Journ. of Preventive Medicine*, August, 1905 (Refs.).

by the pink colour that develops on the addition to the cultivation of a few drops of strong sulphuric or hydrochloric acid.

TUBERCULOSIS of the intestine is a common affection, particularly in cases of phthisis, and sometimes in young children from one to five or six years of age. In children it is regarded as being largely due to infection from tuberculous milk, in phthisis from swallowing the tuberculous sputum.

The main seat of the disease is usually about the cæcum, and the process begins in the Peyer's patches and lymphoid follicles. These are first swollen, enlarged, and raised; then their centres become yellowish and begin to necrose and ulcerate, small ulcers first forming and subsequently coalescing. The large tuberculous ulcer has a ragged base formed of the submucosa infiltrated with tuberculous nodules and caseous *débris*, the outline is irregular, and the edges are sinuous and infiltrated, but slightly undermined, and the long axis is usually transverse to the long axis of the bowel. The process often extends to the muscularis, and may produce a crop of tubercles on the serosa; it seldom, however, perforates, but adhesions and fistulous connexions are not infrequent. Hæmorrhage to any extent is also uncommon. The mesenteric glands are generally enlarged, and frequently infected and caseous. In children, the glands may be affected though little or no lesion, except catarrhal inflammation, of the intestinal mucosa may be present. This sets up wasting and diarrhœa, and the condition is known as *tabes mesenterica*.

In some cases of general tuberculosis the serous coat of the intestine may be infiltrated with tubercles without the mucous membrane being affected.

Fistula in ano is often due to tuberculous ulceration of the rectum, and its connexion with tuberculosis has long been recognised.

SYPHILIS is rare in the bowel, except at the lower part of the rectum and at the anus. Gummata may, however, occur.

The primary sore may occur at or near the anus, and condylomata are common. A syphilitic stricture of the rectum, due to cicatrisation of an ulcer or fissure, occasionally occurs.

ACTINOMYCOSIS is occasionally met with, particularly at or near the appendix.

TUMOURS OF THE INTESTINE.—*Polypi* are frequent in the rectum and large intestine. They usually form fleshy masses from the size of a pea to that of a walnut, and structurally are generally adenomata, occasionally malignant. *Myomata* are sometimes met with and are multiple, and grow from the muscularis. *Carcinoma* is not infrequent and is more common in the large intestine than elsewhere, particularly in the rectum and sigmoid. It is usually a columnar-celled growth, and frequently of an adenomatous type. Colloid and scirrhous cancer also occur (Pl. XV., B.). Cancer of the intestine is relatively frequent in young adults. *Sarcoma* is rare.

ENTEROLITHS, or intestinal concretions, are sometimes met with, generally in the small intestine. They consist of fæcal matter and vegetable *débris* infiltrated with lime-salts. *Inspissated fæces* may collect and form large masses, principally in the sigmoid, even in persons (usually females) without obstruction, and who have more or less regular evacuations, but are generally associated with constipation.

THE LIVER.

The liver is divided into two unequal lobes, a larger right and a smaller left, separated from each other by the umbilical fissure, and on the under and posterior surfaces of the right lobe there are three secondary lobes, the Spigelian, caudate, and quadrate. The organ measures 25–30 cm. transversely, and 15–18 cm. from the posterior to the anterior border, and weighs about 1·5–2 kilograms.

The liver is nearly covered with a peritoneal sheath or serous coat, under which is a fibrous coat, investing the whole gland. This under the serous coat is thin and delicate; it is attached to the hepatic glandular substance, and is continuous with the delicate areolar tissue which invests the lobules. At the transverse or portal fissure (where the great vessels enter and the hepatic duct passes out) it becomes continuous with the capsule of Glisson, which ensheaths the vessels and hepatic duct both here and in their ramifications within the liver substance.

The liver substance is composed of a multitude of small polyhedral lobules 1–2 mm. in diameter, which in man are just distinguishable but which in some animals are definitely separated by areolar tissue. Each lobule consists of a mass of polyhedral cells, with well-defined nuclei and abundant cytoplasm, which appear to be more or less radially arranged about the central point of the lobule. The branches of the portal vein (interlobular veins) and hepatic artery and the bile-ducts pass in sheaths of connective tissue, derived from Glisson's capsule, to the periphery of the lobules. The interlobular veins break up into intra-lobular capillaries in the lobule, from which the intra-lobular or central veins of the lobules take origin. The intra-lobular veins unite to form larger branches, the sub-lobular, which empty into the hepatic veins. The branches of the hepatic artery ultimately join the intra-lobular veins. This double blood-supply of the liver is of considerable importance. For descriptive purposes in pathology, the lobule is divided into three zones: (1) the peripheral third, termed the "portal vein zone," (2) the intermediate third, the "hepatic artery zone," and (3) the central third, the "hepatic vein zone."

The larger bile-ducts are lined with columnar, the smaller with cubical, epithelium.

The liver is developed as a diverticulum from the primitive gut.

The gall-bladder is a pear-shaped membranous sac 7–10 cm. in length and 4 cm. across at the widest part, and has a capacity of 30–40 c.c. The cystic duct, 4 cm. in length, unites with the hepatic duct to form the common bile-duct, which is 7 cm. in length and passes downwards to the duodenum, where, after running for 2 cm. between its coats, it opens by an orifice common to it and the pancreatic duct into the bowel at the junction of the second and third parts of the duodenum. The mucous membrane is covered with columnar epithelium.

The functions of the liver are: (1) the formation of nitrogenous waste materials, urea and uric acid; (2) the formation of glycogen; (3) the interception of various substances, particularly many poisons—*e. g.* metallic salts, alkaloids, and various leucomines and toxins; and (4) the formation of bile, derived indirectly from the blood. Human bile contains 85 parts of water, 10 of bile-salts (chiefly glycocholates with some taurocholates), 3 of mucus and pigments (chiefly bilirubin), 1 part of fats, cholesterin, etc., and 1 part of inorganic salts.

ICTERUS, or jaundice, is a symptom, not a disease *per se.* It is applied to a condition in which the tissues and fluids of the body become stained with bile-pigment, the bile-pigments and in some cases the bile acids being discharged by abnormal paths—*e. g.* the urine, sweat, exudations; but the most noticeable feature is the collection of the pigment in the subcutaneous tissues, so that the skin becomes yellow. Though usually in solution, crystals may be met with in the kidneys and fat. The colour varies from pale canary yellow to deep yellow, or in long-standing cases sometimes to a sort of olive tint. The urine, first yellow, may ultimately become porter-coloured, and stains casts that may be in it and the linen. The universal distribution of the pigment evidently indicates that it is carried by the blood.

Various phenomena often accompany jaundice—dyspepsia, headache, irritation of the skin, slow pulse (probably due to the action of the bile-acids on the central ganglia or heart-muscle), constipation, with pale and offensive stools, and rarely xanthopsy or yellow vision. In advanced cases delirium, coma, etc., may occur, but these are probably due to substances other than the normal biliary constituents.

Jaundice has been described as obstructive or hepatogenous—*i. e.* due to retention of bile from impeded excretion—and non-obstructive or hæmatogenous, in which the pigment is elaborated somewhere in the blood itself. Recent work has shown that hæmatogenous jaundice probably does not exist, and all forms, therefore, are to be considered as hepatogenous, or obstructive. Thus toluylenediamine and arseniuretted hydrogen produce intense jaundice in animals with no evidence of duodenal catarrh. But Hunter has shown that as regards the first-named substance an extensive catarrh of the bile-ducts is present from their origin downwards towards the duodenum, and that obstruction, therefore, is really present. Minkowski and Naunyn have shown that in ducks and geese arseniuretted hydrogen produces no jaundice if the liver be removed—*i. e.* the liver is essential for the occurrence of jaundice. It may be concluded, therefore, that all forms of jaundice are hepatogenous, and due to re-absorption of bile from the liver, primarily by the lymphatics, which discharge the bile-pigment etc., into the blood *viâ* the thoracic duct, ligature of the latter preventing obstructive jaundice.

The nature of the obstruction in jaundice varies. Generally it is due to catarrh of the duodenum and common duct (*catarrhal jaundice*); this constitutes the ordinary attack of jaundice. Pancreatic disease is frequently accompanied by jaundice, either inducing catarrh of the common duct or causing pressure on it, as in cancer of the head of the pancreas. Gall-stones, enlarged glands, generally malignant, in the portal fissure, cirrhosis, and chronic cardiac disease, producing congestion, obstruct the bile-ducts, and cause jaundice. Jaundice also occurs in many infections—*e. g.* septicæmia and yellow fever, in acute yellow atrophy of the liver, with many poisons, etc. In moderate degrees of jaundice the smaller bile-ducts are distended with bile and the liver-cells more or less deeply stained.

Icterus neonatorum, often occurring in new-born children, has received various explanations. By some it is regarded as the result of the changes in the circulation at birth; another theory is that it is due to œdema of Glisson's capsule.

Weil's disease is a condition associated with fever, gastric disturbance, enlargement of liver and spleen, and jaundice. The ætiology is unknown, but it is regarded as toxæmic, perhaps infective, and *proteus*-like bacilli have been isolated. *Infective* and *epidemic jaundice* have also been described.[1]

Malformations of the liver, especially variations in the lobes, are not infrequent, and the organ may be transposed with other viscera. Tight-lacing frequently produces grooves on the surface and depression of the organ.

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[1] See Sandwith, *Brit. Med. Journ.*, 1904, vol. ii, p. 672, and Anderson, *ibid.*, p. 673.

PASSIVE CONGESTION is common, particularly in chronic cardiac disease, occasionally from pressure on the vena cava. The liver is enlarged, engorged with blood, and soft, and the vessels are everywhere distended. Later the liver becomes smaller, and presents the "nutmeg" appearance, the lobules being dark at the centre owing to congestion in the hepatic vein zone, and yellowish at the periphery owing to infiltration of the portal vein zone with fat.[1] Ultimately the liver may be reduced in size, hyperplasia of the connective tissue between the lobules takes place, and the organ becomes pigmented (*cyanotic induration*). *Active congestion* occurs in inflammatory affections.

EMBOLISM and THROMBOSIS of the portal vein may occur, particularly in connexion with infective ulceration of the bowel. They may cause nutritive disturbance and focal necrosis, but infarction is a rare event from embolism, as the circulation is too free. Wooldridge,[2] by injecting a solution of "tissue fibrinogen" (nucleo-proteid) into the portal vein in dogs, was able to produce hæmorrhagic infarction in the liver, and this condition does occasionally occur in man, but is very rare. Thrombosis of the portal vein ensues usually from an infective inflammation of the vein (pylephlebitis) secondary to infective endocarditis, appendicitis, ulcerative colitis, etc. A gradually ascending inflammation and thrombosis of the branches of the portal vein may occur, with multiple abscesses in the liver.

Minute hæmorrhages into the liver are frequently seen in the hæmorrhagic diathesis, infectious traumatism, etc. In leukæmia the liver is infiltrated with leucocytes, which greatly distend the portal capillaries.

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[1] According to Hamilton this is not the case, the yellow colour being due to atrophic liver-cells with abundance of pigment.

[2] See *Collected Papers*, 1893, p. 346.

Simple atrophy of the liver may occur in old age and in various cachexias, particularly in cancer of the œsophagus and stomach (the liver is diminished in size in atrophic cirrhosis and acute yellow atrophy; see below).

Cloudy swelling of the liver-cells is common in many infections and in febrile conditions.

Fatty infiltration and **degeneration** of the liver are not uncommon. The liver is normally a storehouse for fat, and great variations occur in the amount of fat contained in it under natural conditions. Any causes which interfere with the natural removal and oxidation of fat lead, therefore, to an increase in the storage fat, and a condition of *fatty infiltration* results; such are rich diet, inactivity, alcoholism, pulmonary phthisis, phosphorus-poisoning, simple, and particularly pernicious, anæmia, etc. The most advanced fatty degeneration is seen in acute yellow atrophy. Part of the fat may be derived from the transformation of glycogen. At an early stage the liver may be somewhat enlarged and flabby, pale or yellowish. The cells are found to contain fat globbles, particularly in the outer or portal vein zone of the lobules, which thus become more clearly demarcated than usual. In advanced cases the liver is much enlarged, and may weigh 2·5–3 kilograms, soft and doughy, and pits on pressure, yellow, greasy, and decreased in specific gravity to such an extent that pieces may float in water, and the cells of the whole of the lobule may contain fat globules (Pl. XVI., A.).

Lardaceous infiltration.—The liver is one of the commonest seats of the lardaceous deposit, the condition occurring in syphilis, prolonged suppuration, etc. The organ is much increased in size and may be two or three times larger and heavier than normal. It is pale or dull-pinkish in colour, like smoked salmon, and has a somewhat leathery, elastic feel. The general contour is preserved, but the edges tend to be rounded, and the cut surface has a dull lustre comparable to a wax model (Hamilton). Microscopically, it is the middle or hepatic artery zone of the lobules which is principally affected, the lardaceous material being deposited in the walls of the capillaries, but in advanced cases both the outer and inner zones may be involved. The liver-cells which lie between the affected capillaries are more or less atrophic and fatty.

Focal necrosis is common in the liver in various infections, particularly typhoid fever. It occurs as small greyish or yellowish dots in which the cells are necrotic (see p. 18).

Pigmentation occurs under various conditions. In *jaundice* the liver may be of a yellow colour, the liver-cells being stained yellow or occasionally containing crystals of bilirubin. In *malaria* the liver becomes enlarged and dark pigment granules of melanin are seen in the capillary vessels, giving the organ a dull leaden hue. In *pernicious anæmia* and other conditions associated with blood-destruction, an iron-containing pigment (hæmosiderin) is deposited in the cells in the outer zone of the lobules and also in the portal sheaths. It is of a yellowish colour and when treated with potassium ferrocyanide and hydrochloric acid yields Prussian blue. The amount of iron in the liver in this disease may be ten or even twenty times greater than the normal.

Acute yellow atrophy, icterus gravis, is a remarkable disease in which rapid atrophy and degeneration of the liver take place accompanied by grave constitutional symptoms—fever, delirium, hæmorrhages, and jaundice. It is rare in children and old persons, being most common from twenty to thirty-five years of age. It is not infrequently associated with pregnancy.

At a very early stage the liver may be a little enlarged, but it rapidly diminishes in size, and the disease may run a fatal course in ten to fourteen days. The liver is reduced to one half its normal size or less, the capsule is wrinkled, the consistence tough, and the colour usually yellow. The outline of the lobules is not recognisable; here and there patches of liver-cells may have escaped destruction, but for the most part they are converted into a granular and fatty detritus. Numerous hæmorrhages may be found in the skin, serous and mucous membranes; the urine is almost destitute of urea but contains leucin and tyrosin. The ætiology of the condition, which bears considerable resemblance to phosphorus-poisoning, is unknown, but it is probably infective.

HEPATITIS, inflammation of the liver, is of various kinds. *Acute parenchymatous hepatitis* occurs in infective diseases—*e. g.* typhoid.

ABSCESS of the liver, acute suppurative hepatitis, is always infective. It occurs in pyæmia and pylephlebitis, intestinal ulceration, etc., and the abscesses are generally multiple.

TROPICAL ABSCESS of the liver is generally single and is associated with amœbic dysentery. During the period 1870–1895 of forty-five cases of liver abscess treated at the Seamen's Hospital, Greenwich, Johnson Smith states that distinct evidence of dysentery was obtained in thirty-eight (84 per cent.). The fact that these abscesses are commonly single does not support the view that the amœbæ gain access to the liver either by the portal vein or by the bile-ducts. Rogers[1] suggests that the organisms travel from the bowel across the peritoneal cavity, whether there be previous adhesions or no; the usually superficial site of the abscess is in favour of this view. Occasionally the abscesses are multiple, and these may be due to portal-vein or bile-duct infection, but in nearly every case of multiple abscess there is a double infection with amœbæ and pyogenic organisms. In the ordinary tropical abscess the pus is *sterile* and of a characteristic chocolate-brown colour and streaked with blood. No amœbæ are to be found in the pus at the time of operation, but make their appearance in the drainings about three days later—*i.e.* when the wall is beginning to granulate and contract. These abscesses if untreated may rupture into the lung (10·5 per cent.), into the peritoneum (7 per cent.), or into the pleura (5·5 per cent.), or occasionally elsewhere.

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[1] *Brit. Med. Journ.*, 1903, vol. i, p. 1315.

CHRONIC INTERSTITIAL HEPATITIS, or cirrhosis of the liver, is a form of diffuse fibrosis or hyperplasia of the connective tissue, causing secondary changes in the liver-cells and capillaries. Various forms may be distinguished and a number of different classifications have been proposed.[1]

Atrophic portal cirrhosis, hob-nail liver, gin-drinkers' liver, Laennec's cirrhosis, is the common form of hepatic cirrhosis. It is frequently related to alcoholism. Clinically, this variety is characterised by dyspepsia, hæmatemesis, enlarged spleen, ascites and œdema. Jaundice is usually absent, or slight and transient. The liver is small and reduced in weight, it may be to half the normal, and is very tough and inelastic. It is not usually adherent, nor is the capsule appreciably thickened. The surface, instead of being smooth, is covered with nodulations varying in size from a pin's head to that of a bean, and often somewhat quadrilateral in shape. The colour varies; this may be red or often is yellowish or greenish. On section it is seen that bands of fibrous tissue, starting from the depressions on the surface, form a network throughout the organ, enclosing rounded islets of liver-tissue, each islet consisting of several lobules (hence this variety of cirrhosis has been termed "multilobular"). Microscopically, although the outer layer of the capsule is almost unaltered, the inner layer will be found to be considerably thickened. The bands of fibrous tissue encircle, as stated, several lobules, but from the main bands finer strands ramify throughout the islets of liver-tissue (Pl. XVI., B.). The newly-formed fibrous tissue is most abundant in the periportal regions, and at an early stage the portal sheaths may be seen infiltrated with round cells, some of which are fibroblasts, some leucocytes. The fibrous bands are made up of round cells, spindle-cells, and white fibrous tissue in varying proportion according to the age of the lesion. The liver-cells may show little change, but in the neighbourhood of the fibrous bands are generally atrophic or fatty (from infiltration); a certain amount of pigmentation may be present. Within the fibrous bands double rows of cubical cells are sometimes seen (but not to such an extent as in the variety of cirrhosis next to be described) which resemble bile-capillaries, the origin of which is uncertain. They may be derived by proliferation of the bile-ducts, or they may be a reversion of the liver-cells to the biliary type, and this seems the more likely. Blood-vessels are also present in the fibrous bands, but are mainly branches of the hepatic artery, the branches of the portal vein to a large extent being occluded.

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[1] See Rolleston, *Diseases of the Liver* (Saunders & Co.), 1905.

The spleen is generally decidedly enlarged, the capsule is thickened, the capillaries are dilated, and the fibrous tissue is increased in amount.

It is probable that at a very early stage of the disease the liver is somewhat enlarged. Death sometimes is due to toxæmia.

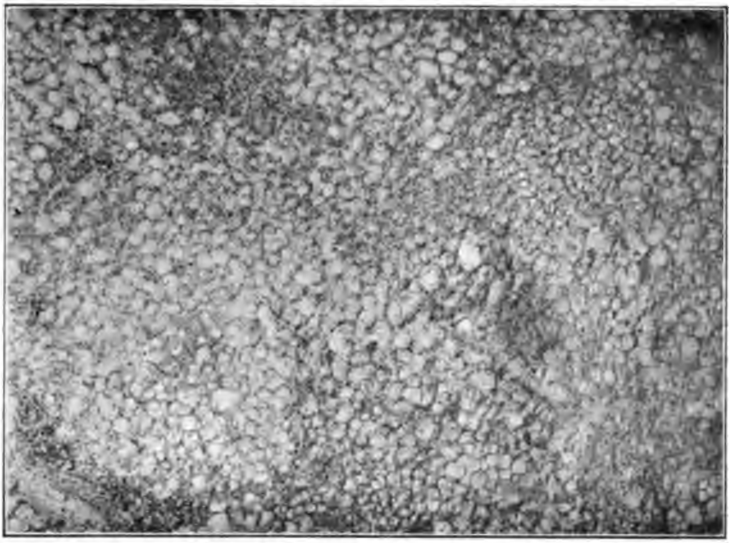
Ætiology of portal cirrhosis.—Portal cirrhosis is undoubtedly related to alcoholism, but not always, children and individuals who do not take alcohol occasionally suffering from it. The administration of alcohol to animals also does not usually induce fibrosis but only fatty change. It has been suggested that constituents other than the alcohol in wine and spirits are responsible for the fibrosis. It is probable that the usual cause is some poison formed in the intestine which reaches the liver by the portal vein, alcoholism being an antecedent, or preparing the way, rather than a *causa vera.*

Arsenic and perhaps other poisons seem capable of inducing cirrhosis. The results of the injection of bacterial toxins are somewhat contradictory, cirrhosis occasionally being produced, but not always. Indirectly, syphilis may play a part in the production of cirrhosis by rendering the liver more vulnerable. Poisons, or perhaps micro-organisms, reaching the liver by the hepatic artery may give rise to changes of a cirrhotic nature. Adami and Miss Abbot have proved the presence of the *B. coli* in the liver in the Pictou cattle disease, which is characterised by marked hepatic cirrhosis.

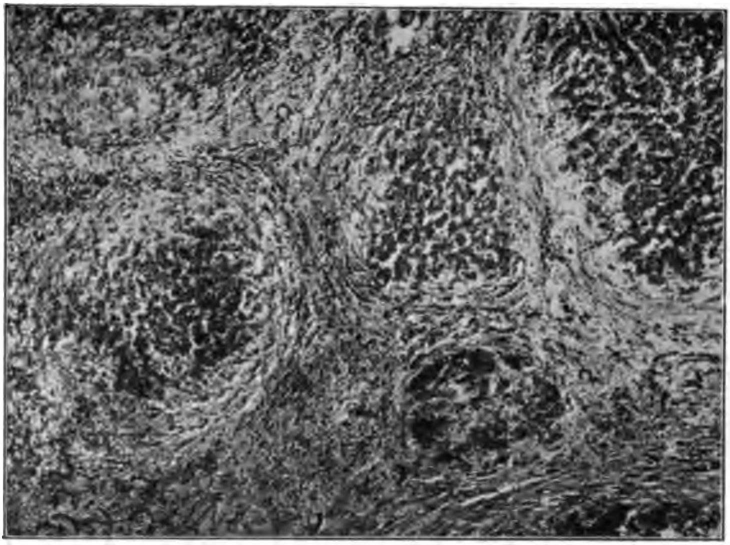
Cirrhosis is usually regarded as being a primary chronic inflammation or hyperplasia of the connective tissue in the portal areas, but by some has been regarded as secondary to primary degeneration and atrophy of the liver-cells. Powell White has suggested that in the smooth cirrhotic livers the fibrosis is really a diffuse fibroma.

Cirrhosis anthracotica.—In rare cases cirrhosis of the liver is associated with the presence of small masses of carbon in the organ, and this condition is analogous to anthraconiosis (p. 310).

PLATE XVI.



A. **Fatty liver.** (Hæmatoxylin and eosin, ×45.)



B. **Cirrhosis of the liver.** (Hæmatoxylin and eosin, × 75.)

To face page 366.

Pigmentary cirrhosis of hæmochromatosis, bronzed diabetes, is a condition in which glycosuria is present, together with an enlarged and cirrhotic liver, in which pigment is present in the cells, and pigmentation of the skin. It is regarded as being due to the action of a hæmolytic agent, perhaps bacterial, with accumulation of pigment in the organs and skin, and secondary fibrosis of the liver and pancreas. The conception of the disease held at present is as follows: For some unknown reason two kinds of pigment accumulate in the body—the so-called hæmosiderin in the epithelial cells of the liver, pancreas, and other glands, and the so-called hæmofuscin in the smooth muscles of the alimentary tract, of the blood-vessels of the genito-urinary tract, etc. As a result of the deposition of the hæmosiderin in the liver and pancreas, the parenchymatous cells of these organs degenerate. This degeneration, together with the direct irritation of the pigment itself, acts as a stimulus to the growth of connective tissue, and hypertrophic cirrhosis of the liver and chronic interstitial pancreatitis develop, the pancreas, as a rule, becoming half again as large as normal. When the chronic interstitial pancreatitis has reached a certain grade (according to Opie, when it has destroyed a sufficient number of the islands of Langerhans) diabetes develops. The diabetes is therefore a terminal phenomenon, and cases have been as a rule rapidly fatal after the diabetic symptoms have appeared. The hæmochromatoses, however, together with enlargement of the liver, may exist for many years without development of diabetes.[1]

Obstructive biliary cirrhosis, hypertrophic cirrhosis, or large cirrhotic liver. Clinically, the picture is one of biliary obstruction. The liver at first may be enlarged but later it contracts, its surface is granular or irregular, and consistence very tough. Microscopically the bands of fibrous tissue encompass the individual lobules (hence this variety has been termed "uni- or mono-lobular"), and send delicate strands into the lobules. The bile-ducts are dilated, sometimes to such a degree as to render the liver honeycombed, and throughout the fibrous tissue are numbers of structures resembling bile-capillaries, which, however, are probably double rows of altered liver-cells and not proliferated bile-capillaries.

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[1] See Barker, *Johns Hopkins Hosp. Bull.,* 1905, xvi, No. 176, p. 385.

The spleen may be small, normal, or enlarged.

This form of cirrhosis is especially seen in cases of obstruction to the outflow of bile—*e. g.* from calculus, cancer, stricture, enlarged glands in the portal fissure, cancer of the head of the pancreas, etc.—but not all cases of biliary obstruction are accompanied by cirrhosis. Ligature of the bile-ducts in animals sometimes is followed by fibrosis and cirrhosis but sometimes not; the fibrosis has been ascribed by Harley and Barratt[1] to the continued slight irritation of the bile.

Hypertrophic biliary cirrhosis, hypertrophic cirrhosis, or Hanot's cirrhosis, is a condition in which the liver is much enlarged in size and weight up to double the normal, smooth or slightly granular, and microscopically there is a unilobular fibrous network and considerable production of so-called bile-capillaries, and the existing small bile-ducts may show proliferation of their epithelium. The fibrous tissue is less in amount and more delicate than in the other varieties of cirrhosis and contains elastic fibres. The spleen may be very large in this variety and weigh from 0·5 to 1·5 kilograms or more. Microscopically, there is a fibrosis, with distension of the vascular sinuses. Clinically, this variety is characterised by febrile attacks and much jaundice, but ascites is usually absent and there is no marked relation to alcoholism as in the portal variety.

It is probably caused by some hæmic infection of a chronic nature leading to inflammatory changes in the liver. Hanot regarded the initial lesion as a catarrhal inflammation of the bile-ducts. An alternative but not such a likely view is that it is a local infection of the bile-ducts, caused by an ascending infection from the duodenum.

Capsular cirrhosis from perihepatitis is occasionally seen. The liver is small and often deformed, the capsule is much thickened and the liver substance cirrhotic.

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[1] *Journ. of Pathol. and Bact.,* vol. vii, 1901, p. 203.

Tuberculosis, syphilis, and malaria (very rare) occasionally induce a cirrhotic condition of the liver.

TUBERCULOSIS.—Primary tuberculosis of the liver is very rare, if it occurs at all, but secondary tuberculosis is frequent; it may be a disseminated miliary, a chronic tuberculous hepatitis, or solitary. The *miliary tubercles* are located for the most part in the periportal connective tissue and appear as minute greyish-yellow points, often bile-stained, and readily overlooked if the liver is fatty.

In *tuberculous hepatitis* there is a diffuse overgrowth of connective tissue in which greyish-yellow tuberculous nodules are situated. *Solitary tubercles,* which are rare, are generally few in number, of some size, and tend to caseate.

SYPHILIS occasions four kinds of changes in the liver, an acute parenchymatous hepatitis, large gummata, miliary gummata, and syphilitic cirrhosis. In the first jaundice may be present and there may be considerable destruction, resembling acute yellow atrophy. Large gummata are frequent in the liver of adults; they are generally met with in the stage of absorption and fibrosis, so that more or less stellate scars are present, which may cause considerable puckering and deformity. Usually they are multiple and scattered; in some cases they may form masses projecting from the surface and simulating malignant growths. Miliary gummata are usually associated with a considerable degree of fibrosis. In infants the subjects of congenital syphilis a diffuse fibroid infiltration is frequent in the form of a periportal unilobular cirrhosis.

ACTINOMYCOSIS has one of its most frequent sites in the liver. It tends to produce numerous small suppurating foci, which may coalesce, and proliferation of connective tissue, so that the affected area becomes divided up by coarser and finer bands.

TUMOURS.—Primary tumours of the liver, with the exception of adenoma and angeioma, are infrequent, but secondary tumours in this organ are common in the course of malignant disease.

Adenoma occurs in normal and cirrhotic livers, and forms nodules of a greyish to brownish colour. Microscopically, it consists of tubular acini lined with cubical epithelium. In some instances a cyst is developed (cystadenoma).

Angeioma of the cavernous type is the commonest of the benign liver tumours. It forms a tumour varying in size from a pea to an apple, is purplish or brownish in colour, sharply defined, and often encapsuled.

Primary carcinoma is the exception. It may occur as a single large mass, or as an infiltrating nodular cirrhosis. It may be a cubical-celled adenocarcinoma or of the medullary type; if there is much fibrosis, it may be a scirrhus.

Secondary carcinoma is much more common than primary. It may be metastatic or arise by extension from the gall-bladder or bile-duct, or from the stomach or intestine if there be previous adhesions. Metastatic growths are frequent, and develop from small masses of cancer-cells carried to the liver by the portal vein or hepatic artery. They form multiple scattered growths, at first small, but later forming nodules as large as a walnut, or ultimately, by fusion, masses the size of an orange. The nodules tend to be more or less spheroidal in shape, and by necrosis and softening of the central portion the surface of each nodule generally assumes an umbilicated form. The nodules may be solid, or hæmorrhagic, and mucoid or cystic degeneration may occur in them.

Primary sarcoma is rare, but *secondary sarcoma*, particularly of the melanotic variety, is not uncommon.

PARASITES.—The liver is one of the most frequent sites of echinococcus cysts, which may be unilocular or multilocular. *Pentastomum denticulatum* and *Fasciola hepatica* also occur.

The Gall-Bladder and Bile-Ducts.

The gall-bladder is occasionally absent, and various abnormalities of the ducts occur.

INFLAMMATION of the gall-bladder (cholecystitis) and bile-passages (cholangitis) is not infrequent, and generally arises by extension from the liver, intestine, or pancreas, or occasionally is hæmatogenous, and occurs in various infective conditions. The organism usually found is the *Bacillus coli*, occasionally the *B. typhosus*, *D. pneumoniæ*, or pus-cocci.

The inflammation is generally catarrhal, but may be purulent, and even gangrenous. Simple catarrh frequently affects the common duct, and particularly its lower end, and leads to biliary obstruction and jaundice. If suppuration occurs, the gall-bladder becomes distended with muco-pus, its outer surface may become covered with a fibrinous exudate, adhesions to neighbouring viscera may form, and perforation may ensue.

BILIARY CALCULI (gall-stones) are common, and consist either of cholesterin, or of bile-salts and bile-pigments, or of a mixture of these. They vary in size from that of a pea to a walnut or larger, and may be single or multiple; occasionally hundreds may be present. When single the calculi are usually spheroidal or ovoid in shape, but when multiple they become facetted and angular. Calculi are twice as frequent in females as in males, and are generally met with after middle life. The causes leading to their formation are not clear, but stagnation and inspissation of bile and slight chronic catarrh play a part. Typhoid bacilli may collect in the gall-bladder in cases of typhoid fever, persist for months, perhaps years, and clumps of bacilli have been found to act as nuclei for the formation of calculi.

Biliary calculi for a time may exist without symptoms, but sooner or later they are apt to give rise to catarrh, cholecystitis, and cholangitis, simple or suppurative, and, passing into the ducts, cause biliary colic; or if a stone becomes impacted, it produces dilatation of the ducts and bladder, obstructive jaundice (if in the common duct), and even necrosis and perforation. Cirrhotic changes in the liver and pancreas may also ensue, and carcinoma of the gall-bladder is frequently associated with gall-stones, the latter being regarded as a predisposing cause. A gall-stone has been known to cause intestinal obstruction, but this is excessively rare. Stenosis of the common bile-duct may be caused by disease of the head of the pancreas (this may closely simulate gall-stones), cicatricial contraction, pressure of enlarged glands and tumours, etc.

The Pancreas.

The pancreas, which is developed from three buds arising from the primitive intestine, is made up of a number of lobules loosely held together by fibrous tissue, and having a general resemblance to the salivary glands, but the glandular cells are more granular. Interspersed among the glandular acini are groups of flattened cells, the islands or islets of Langerhans. These are not regularly disposed throughout the gland, but, according to Opie, average 18·3 in the head, 18·0 in the body, and 34·0 in the tail per 0·5 square centimetre of a section.

The nature of these "islets" has given rise to considerable discussion. By some they are regarded as having a developmental origin different from the rest of the gland and not to communicate with the ducts. They have been supposed to produce an internal secretion presiding over carbohydrate metabolism, and damage to them has been credited as the cause of pancreatic diabetes (see p. 199). Dale,[1] on the other hand, believes that they simply represent a phase in the activity of the gland, and that they are being continuously formed from the secreting glandular acini, and Minkowski considers that they are in close relation with the glandular acini, with which they have a common blood-supply, and that they discharge into the ducts. Two ducts are always present—the duct of Wirsung, which joins the common bile-duct, and the duct of Santorini, which opens into the duodenum a little higher up, and is occasionally not patent. The pancreas is sometimes lobulated and accessory pancreases may be present. In the past a good deal of stress has been laid on the activity of the trypsin of the pancreatic secretion and self-digestion as a cause of some of the pathological conditions—*e. g.* necrosis—met with in the gland. But Bayliss and Starling[2] have shown that the pancreatic secretion is produced only when the gastric hydrochloric acid stimulates the duodenal epithelium to produce a substance, *secretin*, which acts like, though has not the properties of, a ferment, and this is absorbed and carried to the pancreas and there induces secretion. But the secretion contains only inactive trypsinogen, which before it becomes active trypsin must be acted upon by another ferment, *enterokinase*, present in the succus entericus. The pancreatic secretion, therefore, is not active until it is discharged into the duodenum, and there exist in the blood anti-bodies to both trypsin and enterokinase which would neutralise these ferments should any have become absorbed into the circulation. Besides trypsin, which is a proteolytic ferment, there are also present in the pancreatic secretion two other ferments—amylopsin, which converts starch into maltose, and steapsin (lipase), which splits up fats into fatty acids and glycerin. A certain amount of adaptability of the pancreas is also seen as the result of diet; thus ordinarily the pancreatic secretion of dogs has no action on lactose, but after feeding on lactose for some days, a ferment, *lactase*, which has an inverting action on lactose by splitting it into dextrose and galactose, makes its appearance.[3]

Total extirpation of the pancreas produces digestive disturbance, wasting, glycosuria, polyuria, polyphagia—all the symptoms of diabetes, even when carbohydrates are withheld (pancreatic diabetes).

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[1] *Philosoph. Trans. Roy. Soc. Lond.*, 1904, B. 197, p. 25.

[2] "Croonian Lecture," Roy. Soc. Lond., 1904; *Journ. of Physiol.*, 1905, xxxii, p. 129.

[3] See Bainbridge, *Brit. Med. Journ.*, 1904, i, p. 778.

Partial extirpation does not lead to glycosuria. If all but $\frac{1}{5}$ - $\frac{1}{10}$ of the total gland be extirpated, glycosuria may ensue on a carbohydrate-containing diet, but not when carbohydrates are withheld (alimentary glycosuria). It is possible in dogs to *graft* a portion (which is mobile) of the pancreas into the abdominal wall, and when the remainder is removed glycosuria does not follow; if, however, the graft is also removed, glycosuria then results.

Ligature of the duct gives rise to a chronic fibrosis (? interstitial inflammation) of the pancreas, but glycosuria does not result. The islets of Langerhans are stated to be unaffected by this operation.

SIGNS OF PANCREATIC DISEASE.—*Glycosuria* is a common symptom of pancreatic disease (see also p. 199).

Hæmorrhage is often a feature of pancreatic disease. It may occur into the gland (hæmorrhagic pancreatitis, see below), or there may be a general hæmorrhagic tendency, especially if jaundice be also present, due to blood-changes, and any slight blow or prick may be associated with considerable bruising or subcutaneous hæmorrhage.

Fat necrosis, particularly of the omentum and other abdominal fat, is really a saponification or splitting up of the fat into fatty acids and glycerine; the former combine with calcium and produce the opalescent fatty patches characteristic of the condition, which is frequent in acute diseases of the pancreas. This lesion is due to the action of the fat-splitting ferment steapsin, as shown by Flexner (see p. 19). Opie, believing that the ferment may be excreted by the kidneys, suggests a test which depends on the decomposition of pure ethyl butyrate by the ferment and the formation of butyric acid. A specimen of the urine is neutralised with potassium hydrate and divided into two parts, one of which is boiled in order to destroy the ferment if present, and to each are added a few drops of ethyl butyrate and of litmus solution. Both specimens are kept at 37° C. for twenty-four hours, and at the end of that time, if steapsin is present, the unboiled specimen should show a marked acid reaction. Cammidge has also devised a test based on the presence of glycerin in the urine. The urine is boiled with strong hydrochloric acid in order to convert the glycerin into a glycerose, neutralised with lead carbonate, and the glycerose identified by the formation of osazone crystals with phenyl hydrazin.[1]

Altered condition of the stools.—Absence of the pancreatic secretion results in the passage of *clay-coloured stools* which are often bulky.

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[1] For details the original paper must be consulted, *Lancet*, 1904, vol. i, p. 782. The method has been criticised by Ham and Cleland, *ibid.*, pp. 1378 and 1684.

Undigested muscle-fibre (azotorrhœa) and *fat in excess* (steatorrhœa) are also signs of pancreatic inadequacy. In normal stools the fat should not exceed 5 per cent., in pancreatic disease there may be 20 per cent.

Reduction in the amount of ethereal sulphates in the urine has been stated to be a sign of pancreatic disease, likewise a *reduced amount of phosphates* in the urine when on a milk diet (due to non-splitting up of the nuclein constituent of the caseinogen).

Wasting, often rapid, is another sign of pancreatic disease and due to the fact that digestion is inadequate.

Jaundice results from disease of the pancreas involving the common duct at its entrance to the duodenum. It is usually seen in pancreatitis and in malignant disease of the head of the pancreas.

FAT NECROSIS occurs as scattered areas of necrosis, the size of a pin's head to that of a pea, and is generally associated with acute or chronic pancreatitis, tumours, or obstruction of the duct (see p. 19).

ATROPHY.—Simple atrophy occurs in old age and in marasmus and chronic diseases. In many cases of diabetes the pancreas is atrophic, and in interstitial pancreatitis the organ becomes contracted. A type of persistent infantilism has been referred to inadequacy of the pancreas,[1] generally due to fibrosis the result of congenital syphilis.

FATTY INFILTRATION may occur in general obesity, and FATTY DEGENERATION in the course of infective diseases, inflammation, and poisoning with mineral salts.

HÆMORRHAGE.—As already stated, there frequently is a general tendency to hæmorrhage in pancreatic disease, and in infective diseases, purpura, etc., small hæmorrhages may occur into the gland. But a much more important and extraordinary condition is the so-called *hæmorrhagic pancreatitis*, in which the greater part or the whole of the organ, and in some instances the surrounding cellular tissue, becomes infiltrated with blood. In some cases it is due to inflammation, in others it is non-inflammatory, or the inflammation is secondary to the hæmorrhage; the latter is better termed *pancreatic apoplexy*. According to Mayo Robson[1] the following are the causes of this remarkable condition:

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[1] Byrom Bramwell, *Scottish Med. Journ.*, 1904, April, p. 321.

(1) Vascular disease, such as atheroma and fatty degeneration, or alcoholic or syphilitic arteritis.

(2) Injury.

(3) Fatty degeneration of the gland-cells and deposit of fat in the pancreas, the result of alcoholism or of general adiposity.

(4) Fat necrosis in the gland or its vicinity has been suggested by Balser, who has reported several cases in support of his views.

(5) Disintegration of neoplasms, such as cancer or sarcoma, may be the cause of extensive hæmorrhages.

(6) Hæmorrhage from embolism of a pancreatic artery is reported by Molière.

(7) Other causes, such as cardiac and pulmonary diseases, cirrhosis of the liver, hæmorrhagic diathesis, scurvy, purpura, the exanthemata, phosphorus-poisoning, etc., may all give rise to pancreatic hæmorrhage.

(8) Pancreatitis may undoubtedly lead to hæmorrhage. The attack comes on suddenly, with acute pain and collapse, nausea, and vomiting, and the abdomen becomes rigid and tympanitic. The pancreas is firm and infiltrated with blood, and gangrene may ensue or extensive fat necrosis. Death may result from shock or from pressure on the cœliac axis.

Inflammation of the pancreas, especially of the subacute or chronic type, is probably more common than has hitherto been recognised, many of the cases with symptoms of gall-stones being attributable to this condition. The inflammation may be catarrhal, affecting the ducts, or parenchymatous, affecting the substance of the organ, and it may be acute, subacute, or chronic. According to Mayo Robson (*loc. cit.*) it may be classified as follows:

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[1] "Hunterian Lectures," *Brit. Med. Journ.*, 1904, vol. i, pp. 659, 719, 773.

(I) *Catarrhal inflammation.*
  (1) Simple, acute or chronic.
  (2) Suppurative.
(II) *Parenchymatous inflammation* (A) Acute.
  (1) Hæmorrhagic.
    (*a*) Ultra-acute, in which the hæmorrhage precedes the inflammation, the bleeding being profuse and both within and outside the gland.
    (*b*) Acute, in which the inflammation precedes the hæmorrhage, which is less profuse and is distributed in patches through the gland.
  (2) Gangrenous.
  (3) Suppurative (diffuse suppuration).
(B) Subacute.
  Abscess of the pancreas (not diffuse suppuration).
(C) Chronic.
  (1) Interstitial pancreatitis, characterised by proliferation of the interstitial connective tissue.
    (*a*) Interlobular, in which the inflammatory process is localised chiefly at the periphery of the lobules, and the islets of Langerhans are implicated only when the fibrosis has reached an advanced stage.
    (*b*) Interacinar, in which the inflammatory process is diffuse, invading the lobules, separating individual acini and invading the islets of Langerhans.
  (2) Cirrhosis of the pancreas—the most chronic form of interstitial pancreatitis, a combination

of interlobular and interacinar changes, and ending in extreme sclerosis, probably resulting from a long-continued infective catarrh (possibly also from alcoholism). It occurs also in cirrhosis of the liver.

The ætiology of pancreatitis may be classified as follows (Mayo Robson):

(I) *Predisposing causes.*
  (*a*) Obstruction in the ducts, the result of gall-stones, duodenal catarrh, pancreatic calculi, cancer of the papilla or of the head of the pancreas, ulcer of the duodenum followed by cicatricial stenosis of the papilla, ascarides, and lumbrici.
  (*b*) Injury, either from a bruise, as by manipulation in operating, or from a crush, as by a blow in the epigastrium, or from wounding by a sharp instrument.
  (*c*) Hæmorrhage into the gland.
  (*d*) General ailments, such as typhoid fever, influenza, mumps.
  (*e*) Certain anatomical peculiarities in the pancreas or its ducts.
  (*f*) Atheroma or fatty degeneration of blood-vessels.
(II) *Exciting causes.*
  (1) Infection, conveyed either—
    (*a*) From the blood, as in syphilis or pyæmia.
    (*b*) From the duodenum, as in gall-stones, obstruction, or gastro-intestinal catarrh.
    (*c*) By extension inwards from adjoining organs, as in gastric ulcer or cancer eroding the pancreas.
  (2) Irritation, as in alcoholism.

Flexner has shown that the injection of a number of substances, either into the gland substance or through the duct of Wirsung, is followed by acute and often rapidly fatal forms of inflammation, commonly of the hæmorrhagic type, associated with fat necrosis and glycosuria, and sometimes with necrosis, suppuration, or occasionally chronic interstitial changes. The substances employed were sulphuric and nitric acids, caustic alkalies, formalin, artificial gastric juice, and suspensions of *B. pyocyaneus* and *B. diphtheriæ.* Opie lays stress on the retrojection of bile as the causative factor in the production of acute pancreatitis.

According to Mayo Robson (*loc. cit.*) gall-stones in the common duct are a frequent—in fact, by far the most frequent—cause of the various forms of pancreatitis, but acute pancreatitis may occur apart from cholelithiasis. Any gall-stone, or stones, impacted in the pancreatic portion of the duct, or even filling the ampulla of Vater, may be efficient causes of the trouble. It may be asked, Why should not every case of common duct cholelithiasis be complicated by pancreatic inflammation? This is readily explained by the fact that in a certain percentage of cases the common bile-duct and the pancreatic duct open by separate orifices into the duodenum, while in another percentage the duct of Santorini is either the principal outlet for the pancreatic secretion or is of such a size that it can act as an efficient outlet, even if Wirsung's duct becomes obstructed. Besides gall-stones, other factors may lead to obstruction of the pancreatic ducts, to infection of the pent-up secretion, and to the different varieties of pancreatitis. It is possible, also, that infection may extend upwards from the duodenum without preliminary obstruction, apparently by continuity of mucous membrane, catarrhal pancreatitis being then a sequel of gastro-duodenal catarrh. Catarrh may be secondary to infective diseases—*e. g.* influenza and typhoid. In 1·3 per cent. of cases of mumps acute pancreatitis seems to supervene.

TUBERCULOSIS of the pancreas is rare, the solitary caseating being commoner than the miliary form.

SYPHILIS generally gives rise to a diffuse interstitial pancreatitis and is not infrequent in the congenital disease. Gummata also occur.

PANCREATIC CALCULUS is rare. The stones are generally ovoid or rounded, whitish, and consist of calcium carbonate (occasionally phosphate or oxalate), may be single, though generally multiple, and are found in all parts of the duct.

PANCREATIC CYSTS are of several varieties :

(1) *Retention cysts,* due to blocking of the duct by a calculus, cicatricial stenosis, pressure from without, or dislocation of the gland. The most common cause is chronic interstitial pancreatitis. The condition has been termed *ranula pancreatica.*

(2) *Proliferation cysts,* either simple cystic adenoma or carcinoma with cyst formation.

(3) *Hæmorrhagic cysts,* the result of the softening, partial absorption, and encapsulation of a hæmorrhage (like those occurring in the brain after an apoplexy).

(4) *Congenital cystic disease,* analogous to that occcurring in the kidney, has been recorded.

(5) *Hydatid cysts* are extremely rare.

(6) *Pseudo-cysts.*—These are not cysts of the pancreas itself, but arise in its immediate neighbourhood and are due to fluid accumulations in the lesser peritoneal cavity.

PRIMARY CARCINOMA is a rare affection. It usually affects the head of the pancreas and may be of the scirrhous or encephaloid type, but exceptionally is a columnar or colloid carcinoma.

PRIMARY SARCOMA is still more rare and is also more prone to attack the head.

Secondary carcinoma and *sarcoma* occasionally occur.

Adenomata and *lymphomata* have been recorded.

THE PERITONEUM, ETC.

The peritoneum is a delicate connective-tissue membrane containing elastic fibres covered with a layer of endothelial cells on either surface and very freely supplied with lymphatics, which communicate with the abdominal cavity, which is thus practically a large lymph space, and absorption from which is very considerable. The large omentum containing fat and a large vascular supply probably serves to preserve the heat of the abdominal cavity, and may be largely responsible for the transudation of ascitic fluid. Various abnormalities in the folds and fissures of the peritoneum occur and are of importance in the production of internal herniæ. Abnormal length of the mesentery has been assigned as one of the contributory causes of inguinal and other herniæ.

Active hyperæmia of the peritoneum occurs over inflamed viscera and as a result of the sudden diminution of intra-abdominal pressure—*e.g.* from the removal of ascitic fluid.

Passive hyperæmia is common in portal congestion and in obstruction from cirrhosis or chronic pulmonary or cardiac disease. The vessels of the reflexions of the peritoneum and of the great omentum become distended and ascites results. Ascitic fluid is usually a clear straw-coloured fluid, but is occasionally opalescent or milky from the presence of fat derived from degenerated cells or admixture with chyle (chylous ascites). This occurs from intercommunication with, or rupture of, some lymphatic channel or the thoracic duct, and is met with most frequently in filariasis.

Hæmorrhage in the form of petechiæ is common in infective diseases, sepsis, and purpura. Large effusions of blood may occur from the rupture of an aneurysm or of a tubal pregnancy.

Peritonitis, inflammation, may be acute or chronic, and is generally the result of infection. The membrane first becomes congested and red, the serous surface becomes dull and lustreless, and threads and patches of lymph soon form. If the process continues, the exudation is apt to become fibro-purulent or purulent, with large flakes of lymph, matting together of the membrane and coils of intestine, and the formation of a turbid purulent fluid in which float flakes of lymph. Frequently there is relatively little fluid. The infecting organisms in the acute form are most often the colon bacillus, the pneumococcus, pus cocci, or streptococci, in the chronic form the tubercle bacillus or gonococcus.

A primary or idiopathic peritonitis is exceptional, and is generally due to some micro-organism reaching the membrane by the vascular system. The so-called "rheumatic peritonitis" is probably of this nature. More often the peritonitis is secondary to inflammation or perforation of the intestine or of a viscus, or is traumatic. An acute hæmorrhagic peritonitis is occasionally met with and seems to be due to a subacute inflammation, with the formation of abundant new capillaries from which the hæmorrhage occurs.

In all peritoneal infections there is a considerable tendency for bacteria and phagocytes to be deposited in large numbers on the great omentum, although the peritoneal exudate may be nearly sterile. Shortly after (15 minutes) an experimental infection, the chief cells found in the exudate are small lymphocytes and coarsely granular eosinophiles, but later the polymorphonuclear cells predominate. The eosinophiles in such cases seem to be phagocytic. The *Staphylococcus albus* can frequently be cultivated from the great omentum, both under normal conditions and also after infection with other bacteria.[1]

Tuberculous peritonitis is commonly a part of general tuberculosis, miliary tubercles being formed on both layers of the peritoneal membrane, especially along the course of the vessels. It may also be secondary to tuberculosis of the intestine, Fallopian tubes, etc.

Tumours.—Primary tumours of the peritoneum are the exception. Lipomata may occur, derived from the omentum or appendices epiploicæ. Retroperitoneal lipoma is generally a mixture of fibrous, fatty and mucoid tissues, and tends to become sarcomatous. Endotheliomata, dermoids and teratomata, and echinococcus cysts occasionally occur. Secondary growths of carcinoma and sarcoma are common.

BANTI'S DISEASE.—This is a condition associated with (1) enlarged spleen and anæmia, (2) interstitial hepatitis, not conforming to any of the usual types, and (3) ascites. The enlargement of the spleen is due to a fibro-adenitis. The ascites does not seem to be dependent on the hepatitis. Hæmorrhages from the mucous membranes and into the skin are frequently a prominent feature. The ætiology of the disease is uncertain, possibly it is infective.

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[1] Dudgeon and Ross, *Brit. Med. Journ.*, 1905, vol. ii, p. 1043.

CHAPTER XVI.

DISEASES OF THE URINARY SYSTEM—DISEASES OF THE MALE GENERATIVE ORGANS.

THE URINARY SYSTEM.

The Kidneys and Urine.

The kidneys vary somewhat in size and position. They measure 10-12 cm. in length, 5–5·5 cm. in width, and 3·4 cm. in thickness, the left being usually somewhat larger than the right. They weigh, the right 110–120 grms., the left 120-130 grms.; in women the weight is 5-10 grms. less. The right lies a little lower than the left. The surface of the kidney is smooth, but in infants and young children may be somewhat lobulated (the fetal condition) and this condition may persist. The kidney is invested with a thin, smooth, but firm capsule consisting of dense areolar tissue with numerous elastic fibres, and can be easily detached from the organ (leaving a perfectly smooth surface) to which it adheres by fine processes of connective tissue. Underneath the capsule is an incomplete layer of unstriped muscle. The organ on section presents a cortical and a medullary portion, the latter forming conical "Malpighian pyramids" which terminate as prominent papillæ in the calices. These pyramids in the fetus are distinct lobules, but in the adult are almost fused save for delicate striæ, prolongations from the capsule, the "columns of Bertini." Normally the ratio of the thickness of cortex to medulla is 1 : 3. The calices unite into two or three primary divisions and these again into the funnel-shaped pelvis which is continued into the ureter. The pelvis and ureter consist of a tough external fibrous and elastic coat and a delicate internal mucous coat which is reflected over the summit of each papilla, and between the two a double muscular layer of longitudinal and circular fibres.

The secreting structure consists of urinary tubules which commence in the cortex in a globular capsule, "Bowman's capsule," lined with a layer of flattened epithelium, which is reflected over and surrounds a tuft or glomerulus of blood-vessels, the whole forming a "Malpighian body." The tubules are first convoluted and lined with a cubical epithelium, then become narrowed and proceed towards the base of the pyramids, return again towards the cortex, forming the "loops of Henle," in which the epithelium is more flattened, once more become convoluted, the "second convoluted tubules," where the epithelium is again more cubical, and these end in short narrow tubules, several of which enter the straight tubes nearly at right angles; the latter descend and unite with one another and open as excretory tubes at the apex of the papillæ. The epithelium of the straight tubes is cubical or somewhat columnar. Besides the vessels of the glomerulus, branches of the renal artery form arches around the apex of the pyramids from which the vasa recta ascend and form a capillary network around the straight tubes. The ureters are 35–37 cm. in length. The epithelium of the pelvis and ureter is stratified like that of the bladder.

Development of the Urinary and Generative Organs.

The urinary and generative organs arise in connexion with a portion of mesoblast known as the "intermediate cell-mass." Some of the cells constituting this are derived from an invagination of epiblast, become differentiated, and ultimately form a tubular structure, the *Wolffian duct*. Posteriorly this opens into the cloaca, anteriorly it becomes connected with invaginations of peritoneal epithelium, between which are vascular glomeruli. The latter constitute the *pro-nephros*; this is permanent only in the lowest fishes, and in mammals is a transient structure. Along the inner side of the pronephros a series of transversely coursing tubes develop in the intermediate cell-mass; these are connected for a time with involutions of peritoneal epithelium, acquire glomeruli, and form the mesonephros or *Wolffian body*. Along the outer side of the Wolffian body another duct develops, the *Müllerian duct*, which also opens out into the cloaca. From the lower end of the Wolffian duct a hollow protrusion or bud grows upwards into a mass of mesoblast continuous with that of the Wolffian body, and with it convoluted tubes and glomeruli become connected and the mass forms the *meta-nephros*, or permanent kidney. The stalk of the bud forms the ureter. The ureter, renal pelvis, and at least the collecting tubules are epiblastic; the renal capsule, intra-renal connective-tissue, vessels, and glomeruli, and possibly the convoluted tubules, are mesoblastic.

In the *male* the Wolffian duct forms the epididymis, the vas deferens, and common ejaculatory duct, also the vesiculæ seminales, which arise as diverticula. A cystic space or hydatid sometimes seen at the head of the testicle may represent the pro- and part of the meso-nephros. The Müllerian ducts form the uterus masculinus in the prostate.

In the *female* the Müllerian ducts form the Fallopian tubes and (by fusion) the uterus and vagina.

The Wolffian duct forms the duct of Gaertner and the parovarium. The renal Wolffian tubules may persist as the paroophoron which lies between the ovary and uterus.

The bladder is derived from the cloaca, except the apex, which is derived from the allantois.

The URINE is clear and transparent, depositing as it cools a delicate flocculent cloud, the so-called "mucus" or "nubecula," consisting of a few epithelial cells, mucus corpuscles, and urate granules. It is usually acid, the acidity being due to acid phosphates, of a specific gravity of about 1018, but this may vary according to concentration from 1002 to 1040. When concentrated, or if they be in excess, the urates may form a reddish deposit (*lateritious deposit*) as the urine cools, but redissolve if it be heated. A neutral or alkaline urine which sometimes occurs physiologically may deposit a whitish cloud of earthy (calcium and magnesium) phosphates which does not redissolve on heating, but dissolves on the addition of acetic acid. On heating urine a similar white cloud of earthy phosphates sometimes appears, which is soluble on the addition of a drop or two of acetic acid, thus distinguishing it from albumin.

The volume of urine daily excreted amounts to about 1500 c.c. It contains about 4 per cent. of solids, and the average composition on a mixed diet of a twenty-four hours' specimen of 1500 c.c. is represented by the following table[1]:

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[1] Hammarsten's *Text-Book of Physiological Chemistry.*

Water	1430 c.c.
Total solids	60 grams.

Organic constituents = 35 grams.

Urea	30 grams (2 per cent.)
Uric acid	0·7 gram.
Kreatinin	1·0 „
Hippuric acid	0·7 „
Other substances	2·6 grams.

Inorganic constituents = 25 grams.

Sodium chloride	15 grams (1 per cent.)
Sulphuric acid, H_2SO_4	2·5 „
Phosphoric anhydride, P_2O_5	2·5 „
Potassium, K_2O	3·3 „
Ammonia, NH_3	0·7 gram.
Magnesia, MgO	0·5 „
Lime, CaO	0·3 „
Other substances	0·2 „

It also contains about 15 volumes per cent. of gas, chiefly carbon dioxide with a little nitrogen.

Normal Constituents of the Urine.

UREA, $CO(NH_2)_2$, or carbamide, is metameric with ammonium isocyanate. It is much less abundant in the urine of herbivora than in that of carnivora and man. It crystallises in four-sided prisms which are colourless and readily soluble in alcohol and in water. It forms a compound with nitric acid, which is sparingly soluble in water containing nitric acid, and it is this compound which sometimes crystallises out as a pale brownish mass, rendering the contents of the test-tube almost solid, on adding nitric acid to a concentrated or febrile urine. It also forms a sparingly soluble compound with oxalic acid, which crystallises as rhombi or six-sided prisms or plates. It is decomposed into nitrogen, carbon dioxide, and water on treatment with an alkaline solution of sodium hypobromite, and this reaction is made use of clinically for estimating the amount in urine. Urea is derived principally from amido-acids, such as leucin, tyrosin, and glycin, which are formed as a result of pancreatic digestion of proteids, also to a small extent from diamido bodies, such as arginin, and from ammonia. The seat of the conversion of these substances into urea is the liver; no other organ or tissue has up to now been proved to form urea.

The elimination of urea varies with the amount of proteid taken as food; it is greatest on a purely meat diet, lowest (less even than during starvation) on a non-nitrogenous diet. In diseases of the kidney in which the integrity of the epithelium of the convoluted tubes is disturbed or destroyed the quantity is much reduced; the amount of urea serves therefore as an index of the efficiency of the kidneys.

In certain diseases of the liver—*e. g.* cirrhosis, acute yellow atrophy, and in phosphorus-poisoning—the quantity is also reduced.

The elimination is increased in all conditions in which the proteids of the body undergo consumption—*e. g.* in fever and diabetes. In the crises which occur in some fevers there may be a critical discharge of urea.

PURIN BODIES AND URIC ACID.—Purin or alloxuric bodies are derived from a compound *purin,* $C_5H_4N_4$. The chief members of the group are uric acid, xanthine, hypoxanthine, adenine, and guanine; theobromine and caffeine also belong to it. In urine the purin bodies are uric acid, xanthine, hypoxanthine, and traces of others. The total quantity of the purin bodies, *excluding uric acid,* voided in the urine is variable, but averages about 30 milligrams *per diem.* These purin bodies are derived either from food, in which they may exist as such or as nucleins (the "free" and "bound" purin), or from destruction of nucleins in the body (p. 190).

Xanthine, $C_5H_4N_4O_2$ (dioxypurin), has occasionally been found as a urinary sediment or calculus, *Hypoxanthine*, $C_5H_4N_4O$, is oxypurin.

Adenine, $C_5H_5N_5$ (aminopurin), occurs in leukæmic urine.

Uric acid, $C_5H_4N_4O_3$ (tri-oxy-purin), is much more abundant in the urine of birds and reptiles than in that of mammals. It is a weak dibasic acid, sparingly soluble in water (1 part in about 39,500 parts at 18° C.) and insoluble in alcohol and ether, but easily soluble in alkaline solutions and in solutions of alkaline phosphates. It crystallises in small rhombic prisms or plates. In the urine it is frequently met with, forming microscopic crystals pale brown in colour, of very varying shape, the commonest being the whetstone, rhombic prisms, dumb-bells, or rosettes of prismatic crystals (Fig. 11, *f*). Heated with a little nitric acid on a piece of porcelain to dryness and then touched with ammonia, it gives a fine purple colour (murexide). In concentrated urine as this cools urates come down as a pink or reddish amorphous deposit, soluble again on warming, consisting of a mixture of potassium, sodium, and ammonium urates. Uric acid reduces cupric oxide on prolonged boiling (several minutes), but not solutions of bismuth, points to be noted when testing for sugar.

Macroscopically, the uric acid crystals are reddish, forming the "cayenne pepper" deposit. If urine be acidulated with hydrochloric acid and allowed to stand for twenty-four hours, the uric acid is deposited as dark brown granules.

Uric acid is formed from nucleins and purin bodies, not from proteids unless they contain these substances, and a vegetable diet does not necessarily reduce the amount. On a farinaceous diet the amount formed is lessened and is but little affected by the addition of a large amount of proteid in the form of egg-white. Meat and sweetbread (thymus, testis, etc.), and cellular tissues generally (*i. e.* containing nuclein), on the other hand, increase the output. The seat of conversion of the purin and other bodies into uric acid is not known with certainty, but is probably the liver. The liver and muscles, perhaps other organs, have also the power of *destroying* uric acid, so that the amount of this substance eliminated is not a certain index of the amount formed.

The variations in the amount of uric acid in disease are not fully known. In fever it is generally supposed to be increased, but this is uncertain. In gout the elimination is probably diminished; there is no increased formation. The only disease in which there is certainly an increased formation is leukæmia.

Kreatinin, $C_4H_7N_3O$, is generally considered to be the anhydride of kreatin which is found in muscle. From 1 to 2 grams are excreted daily. It forms white prismatic crystals readily soluble in water, and, in the presence of sodium acetate, forms with mercuric chloride a double salt, which comes down on standing as spherical globules. It acts as a reducing agent. With picric acid in the presence of alkali, it gives a ruby-red colour (this should be borne in mind when testing for sugar by the picric acid test); with cupric hydrate it forms a soluble, colourless combination, and cuprous oxide is precipitated only on prolonged boiling. It does not reduce an alkaline bismuth solution. The quantity of kreatinin excreted depends on the amount of food, and decreases in starvation; it varies, as a rule, with the quantity of urea, and it seems to be increased when metabolism is increased, as in fever, and decreased with diminished metabolism, as in anæmia and cachexia.

Hippuric acid, $C_6H_5.OC.NH.CH_2.COOH$ (benzoyl amino-acetic acid), occurs in large amounts in the urine of herbivora, but only in small quantity in that of carnivora (about 0·7 grm. *per diem* for man). It decomposes on heating into benzoic acid and glycocoll, and, on the administration of benzoic acid, appears in the urine; the question of the formation of hippuric acid therefore resolves itself into that of the origin of benzoic acid. The latter may arise from aromatic radicles in proteins, especially during putrefactive changes in the intestine, or from similar compounds in vegetables and fruits. The benzoic acid so derived combines with glycocoll, which also arises from proteins in the body, the synthesis being performed by the kidneys (see p. 412). The variations of hippuric acid in disease are unknown.

Oxalic acid, $HOOC.COOH$, occurs physiologically only in small amount, about 0·02 gram *per diem.* It is regarded as being present in the urine as calcium oxalate which is kept in solution by acid phosphates. It occurs in many vegetables and fruits, and also may possibly be derived from proteid. It is a frequent constituent of urinary sediments and calculi in the form of calcium oxalate, which is insoluble in water and acetic acid, but is dissolved by hydrochloric acid, and crystallises in the well-known octahedra, which may be united to form dumb-bells (Fig. 11, *h*).

Ethereal sulphuric acids.—These are organic radicles combined with sulphuric acid—*e. g.* phenol and cresol, indoxyl and skatoxyl, and are found in varying but small amounts (0·1–0·5 grm. *per diem*) in normal urine. The sulphuric acid is so united with the radicles that it does not give the usual reactions. The ratio of the sulphate-sulphuric acid to this conjugated sulphuric acid is about as 10 : 1 in health. The ethereal sulphates are derived from the putrefactive decomposition of proteids in the intestine. They are increased in conditions in which there is putrefactive decomposition of the contents of the bowel or if foul abscesses be present; they are diminished on a milk or carbohydrate diet.

Indol appears in the urine as indoxyl sulphuric acid (indican), $C_8H_7NSO_4$, is derived from the putrefactive decomposition of proteids in the intestine, and amounts to 5–20 milligrams *per diem*. It is increased in quantity in intestinal obstruction, particularly in that of the small intestine. It may be detected by adding to the urine an equal volume of hydrochloric acid and then drop by drop a freshly prepared solution of chloride of lime (= a hypochlorite). This causes a dirty-brown or bluish colour, or precipitate, according to the quantity present, due to indigo, which may be extracted by adding a little chloroform and shaking.

URINARY PIGMENTS.—The natural colour of urine is due probably to several pigments, but principally to *urochrome*, and small quantities of hæmatoporphyrin, uroerythrin occasionally, and urobilin, which is derived from a chromogen by the action of light and air.

Urobilin is an iron-free derivative of hæmoglobin, is identical with stercobilin of the fæces, but is distinct from hydrobilirubin (with which it has been asserted to be identical), and is under physiological conditions probably derived from bilirubin. It is increased in cases where there is internal hæmorrhage, in diseases associated with blood-destruction, and by the action of certain poisons—*e.g.* antipyrin—in fever and in atrophic hepatic cirrhosis, and seems to be the cause of the yellow staining of the skin which is sometimes seen in pernicious anæmia, internal hæmorrhage, and hepatic cirrhosis, the urine being free from bile-pigments.[1]

Uroerythrin is the pigment which gives the pink or reddish colour to urinary sediments. It is increased by muscular activity, excessive eating, or alcoholic drinks, in fever, and disturbance of the liver.

Various other organic substances occur in traces in normal urine, many of which are much increased in pathological conditions, and will be more conveniently discussed when dealing with the abnormal constituents of urine.

Chlorides.—The chlorine is present in urine for the most part as sodium chloride and amounts to about 10 to 15 grams of NaCl *per diem.* Its chief source is from food. It is diminished in fever and diarrhœa, and practically disappears in acute pneumonia.

Phosphates amount to about 2·5 grams of P_2O_5 *per diem.* They exist as dihydrogen and monohydrogen salts, and are mainly derived from phosphates in the food, but a portion originates from nuclein, lecithin, and other organic phosphorus compounds. They are increased in conditions attended with destruction of leucocytes, and in such the curve of increase often closely follows that of the uric acid, and as the leucocytes, particularly the polymorphonuclears, are diminished so the phosphates increase.[2] The phosphatic cloud (phosphate of lime) which so often appears on boiling urine is generally considered to be formed by a disturbance of the balance between the various phosphates whereby the phosphate of lime is kept in solution. But Shattock considers that it is due to the liberation of ammonia from a slight decomposition of the urea by the heating.

Sulphates are derived to a small extent from sulphates in the food, mainly from the oxidation of the sulphur of proteid during metabolism. As stated above (p. 391), they exist partly as sulphate and partly as ethereal sulphuric acid.

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[1] Theile, *Path. Soc. Trans.*, vol. liv, 1903, p. 62.

[2] Williamson, *Path. Soc. Trans.*, vol. liv, 1903, p. 265.

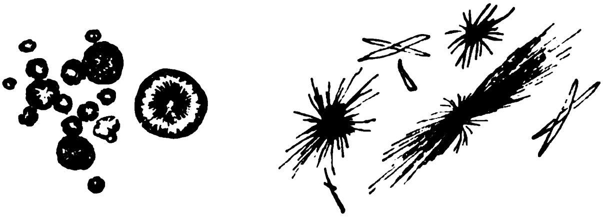
Potassium and *sodium* are eliminated to the extent of 3–4 grams of K_2O and 5–6 grams of Na_2O daily. They are derived from the food. During starvation and fever the potassium is relatively increased.

Ammonia is eliminated to the extent of 0·7 gram of NH_3 daily, and constitutes 4·5–5·5 per cent. of the total urinary nitrogen. It is formed by the digestive glands in the stomach, intestine, and pancreas from proteid. The amount is increased by mineral acids, in phosphorus poisoning, and in diseases of the liver—*e. g.* cirrhosis and acute yellow atrophy. Urea, as stated above (p. 388), is partly derived from ammonia, and a portion, though perhaps not all, of the ammonia in the urine represents a surplus which has escaped this conversion.

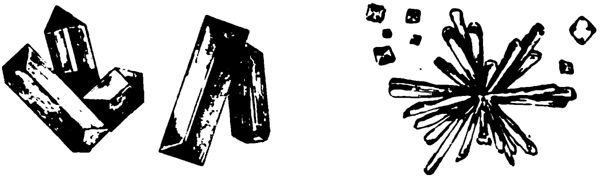
In cases of cystitis it is not infrequent to have a highly ammoniacal condition of the urine. This is due to the decomposition of urea through the agency of bacteria which produce hydrolysis, thus:

$$CO(NH_2)_2 + 2H_2O = (NH_4)_2CO_3.$$

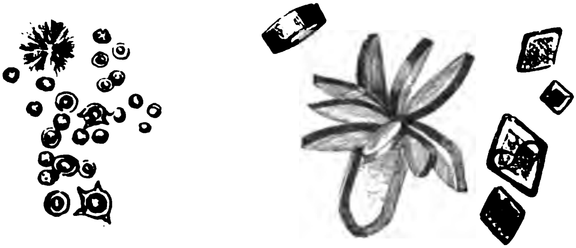
The introduction of the bacteria usually occurs through catheterisation, or by extension along the urethra as a result of an unhealthy condition of the mucous membrane induced by the irritation of a calculus, or of stagnant urine and unemptied bladder in prostatic hypertrophy. Many bacteria have the power of causing this hydrolysis of urea, particularly the *M. ureæ.* Shattock has also shown that the *M. pyogenes aureus* and *albus* have a like power, but not the streptococci. The fermentation is not direct, but is brought about by a ferment which has been termed *urease,* which may be obtained by



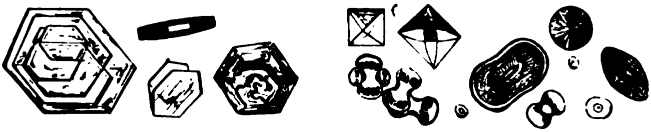
a. Leucin. × 215. *b*. Tyrosin. × 130.



c. Ammonio-magnesium phosphate. × 45 *d*. Phosphate of lime. × 130.



e. Sodium urate. × 215. *f*. Uric acid. × 215.



g. Cystin. × 215. *h*. Oxalate of lime. × 215.

FIG. 11.—Urinary crystals. (Modified from Lionel Beale's *Urinary Deposits.*)

precipitating the viscous material of the urine of cystitis or the microbes from active cultures in urine with alcohol, and extracting the precipitate with water; the extract brings about hydrolysis in a solution of urea with the formation of ammonia.

Calcium and *magnesium* occur as phosphates, which are kept in solution by the alkaline phosphates. Ammonio-magnesium phosphate, or triple phosphate, occurs in the urine, as the well-known prism-shaped crystals (Fig. 11, *c*) and phosphate of lime, occasionally in stellate or rhombic masses (Fig. 11, *d*).

Iron occurs only in traces and as an organic compound, probably a chromogen.

Abnormal Constituents of the Urine.

PROTEID.—Proteid, if present at all in normal urine, is in inappreciable quantity only. Traces of a substance apparently nucleo-albumin and easily mistaken for mucin are not infrequent. In pathological conditions proteids are of frequent occurrence—usually serum albumin, rarely proteoses or peptones. When serum albumin and globulin are present the condition is known as *albuminuria*; when proteoses, *albumosuria* (formerly *peptonuria*); when blood is present, *hæmaturia*, or if blood-pigment alone, *hæmoglobinuria*.

ALBUMINURIA.—Albumin (as it is usual to term the mixture which is generally present of serum albumin and globulin) appears in the urine in a variety of conditions:

(1) Alteration in the circulation of the kidney, generally venous congestion, as in cardiac disease, particularly mitral stenosis, from pressure on the renal vessels in ascites, by tumours or the gravid uterus, and in asphyxial conditions, accompanied with a rise of

venous blood-pressure. This form is known as *congestive albuminuria.*

(2) *Renal albuminuria.*—Albumin makes its appearance in the urine in pathological states of the kidney, which may vary from a slight and transient affection, such as is so common in any febrile condition, to the gross structural alterations which are present in Bright's disease. Bacterial toxins vary much in their poisonous action on the renal structures. In pneumonia, typhoid fever, measles, etc., their effect is usually slight and recovered from, while in scarlet fever and diphtheria serious and lasting damage may ensue and pass into acute nephritis. Many substances are renal poisons, such as cantharides, turpentine, phenol, metallic salts and oxides (see p. 429).

(3) *Physiological, functional,* and *cyclical albuminuria.* —The term "physiological albuminuria" has been used to describe a condition in which, without any symptoms of ill-health, variable amounts of proteid are present in the urine. As it is extremely doubtful whether such can occur with a perfectly healthy kidney, the term "functional albuminuria" is preferable. It is met with chiefly in young adults, particularly after prolonged muscular exercise, as the result of cold bathing, or after certain diet. Frequently albumin is absent when first rising in the morning, appearing as the day goes on. Nervous diseases, such as epilepsy, may also lead to a transient albuminuria. It is probable that in all these cases the kidney is below par; in muscular exercise the products of excessive metabolism may be toxic, after cold bathing there may be renal congestion, in epilepsy vascular derangement. In some instances the proteid appears at more or less definite intervals with a regularity which has led to this variation being termed "cyclical albuminuria." Such cases may go on for

years without the slightest indication of renal disease. The writer knows a case, a delicate male, in whose urine albumin has been detected at intervals during the last twenty years, and who still to all appearances is perfectly free from renal disease. Such cases are, however, the exception, and the detection of albumin in the urine is always a cause for anxiety. Care must always be exercised in these cases to exclude *admixture* of proteid with the urine, such as might result from a gleet, seminal emissions, leucorrhœa, etc.

Gowland Hopkins has related a case in which the albuminuria was closely related to diet, and the proteid present varied in nature with the diet; for instance, on a diet of bread and milk the proteid contained no loosely combined sulphur, whereas on ordinary diet this was always present.

(4) Albumin may be present in the urine from *admixture* with fluids containing proteid—*e. g.* pus, lymph, blood, and inflammatory exudation from any part of the urinary tract. This condition is not usually termed albuminuria.

(5) After injection of egg-albumin proteid appears in the urine, and may even do so after a diet rich in eggs.

The so-called albumin in the urine is usually a mixture of serum albumin with a varying proportion of serum globulin, and the amount of the two together rarely exceeds 1 per cent.; in many forms of renal disease it is far less than this, though occasionally it may rise as high as 4 or 5 per cent. In rare cases the amount of globulin may exceed that of the albumin; now and then the globulin only may be present. This was so in a remarkable case observed by Bramwell and Paton, and curiously enough this proteid separated in a crystalline form. Attempts have been made to correlate the variations in the two proteids with varying amount of structural alteration, but it is possible to lay down only general rules in this respect. Thus Halliburton states:[1]

(1) That in the great majority of cases albumin is more abundant, often much more abundant than globulin.

(2) That this is much more marked in slight cases and in cases of so-called physiological albuminuria than in severe cases.

(3) That a high proportion of globulin usually indicates severe disease of the kidney.

(4) That when both proteids are present there is usually found a rough correspondence between the proteid quotient of the blood and that of the urine.

(5) That the proteid quotient of the blood is a very variable quantity. It varies in different animals and in the very same animal or person at different times, and such differences are not proved to be related to differences in the kind of nutriment ingested.

(6) That the proteid quotient in the urine is still more variable than that in the blood, and that these variations do not necessarily correspond to variations in the proteid quotient of the blood.

In albuminuria, if it be desired to watch the variations in the amount of proteid and the progress of the case, it is necessary to examine twenty-four-hour specimens of the urine and to determine the percentage amount of proteid. For, obviously, the amount of proteid will apparently be diminished if the urine be freely secreted, and not infrequently the morning urine will contain less proteid than that secreted later in the day.

It is a remarkable fact that the fibrinogen hardly ever appears in the urine (*fibrinuria*), though if present its existence is unmistakable as it becomes converted into fibrin. It is seen in chyluria and, of course, if there be hæmorrhage, but practically never otherwise. An explanation of this fact will be suggested later. The pathology of albuminuria is still somewhat uncertain. Formerly it was supposed that the proteids of the blood became changed in conditions associated with albuminuria and that the changed albumin filtered easily through the kidney, but this theory is disproved by the fact that when albuminous urine is injected into the circulation of normal animals the albumin is not excreted by the kidney.

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[1] "Discussion on Albuminuria," *Path. Soc. Trans.*, vol. li, 1900, p. 128. (Much information is there given by many authors.)

The questions to be considered are: (1) Does the proteid pass into the urine because the renal vessels and epithelium are more permeable, or is it actively secreted by the renal epithelium? (2) Through which of the renal structures does the proteid escape?

In acute renal congestion and inflammation there can be little doubt that the same causes which lead to transudation from vessels in inflammation generally, lead to transudation from the renal vessels, and in acute Bright's disease the œdema and dropsy which occur are a proof of the alteration in the vessels, and the same holds good for passive congestion. At the same time, since the normal renal epithelium can secrete a foreign proteid such as egg-albumin, the possibility of a secretory action by the renal epithelium cannot altogether be denied. The influence of filtration in determining the passage of the proteid is well shown by some experiments by Brodie.[1] Making use of a porcelain filter impregnated with gelatin to render it less permeable, it is possible to separate proteoses from serum. The proteoses pass through, being relatively small molecules; the serum albumin and globulin are kept back, being relatively large molecules. Varying the strength of the gelatin and, therefore, the size of the pores of the filter, it is possible to obtain albumin free from globulin—*i. e.* the globulin molecule is larger than the albumin one. Using the excised kidney and perfusing through it blood-serum containing hæmoglobin, Brodie found that first hæmoglobin appeared in the fluid draining from the ureters, then as time went on and the kidney became more and more damaged, albumin appeared, and lastly globulin. Using a dead kidney (one excised and immediately perfused with warm methylated spirit) and perfusing with diluted serum or egg-white, Brodie found that now and then a proteid-free perfusate was obtained; generally, however, proteid was present to the extent of one or two hundredths of the amount in the serum or egg-white solution. He therefore concludes that the absence of proteid from normal urine is solely due to the size of the pores in the filtering membrane of the glomerulus.

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[1] **Discussion at Path. Soc. Lond.,** ***loc. cit.,*** **p. 152.**

He sums up his conclusions thus: The results obtained by these experiments tend to support the explanation given as to the relative frequency of the appearance of the two chief blood-proteids in cases of albuminuria. Hæmoglobin will not appear in the urine unless hæmoglobin is dissolved in the blood-plasma, a condition of things which does not occur in ordinary cases of chronic Bright's disease. When the wall of the kidney tubule becomes partially impervious, then the proteid which has a small molecule passes through—*i. e.* the albumin rather than the globulin. The mere fact that the globulin is kept back whilst the albumin is allowed to pass through might indicate how far the kidney tubule is diseased. If this view be correct, the occurrence of albumin alone would indicate that we still have a practically complete membrane, though one in some way or other pervious to certain proteid molecules. Whether the membrane has become pervious because of a change in the epithelial cells, or because of a change in the cement substance between the cells, is a point which it would be extremely difficult to decide, though it is one which may be of very great importance. There can be no question that where the epithelial cells were actually shed the proteids present would retain the relative proportions which they held in the blood. An intermediate condition would be a case where both these abnormalities were present, and would be indicated by the presence of both proteids, but albumin in a higher proportion than the globulin.

To sum up—in albuminuria there is first a transudation through the vessel-walls, but this transudation will not appear in the urine until the renal epithelium is damaged and rendered more permeable. If there is slight damage to the glomerular epithelium, a little albumin will pass through; when the damage is greater, and especially when the tubular epithelium is also damaged, both albumin and globulin pass through, the former being relatively more abundant; and when the damage is excessive, the ratio of albumin to globulin will approximate to that of the blood. This conception is borne out by experience in disease. In chronic parenchymatous nephritis, in which the tubules are extensively affected, the amount of proteid in the urine is usually large; in chronic interstitial nephritis, in which the glomeruli are primarily affected and the corresponding tubules undergo atrophy, the amount of proteid is usually small. Ribbert has shown that if egg-albumin be injected into an animal, and while the proteid is being excreted the kidneys be excised and placed in absolute alcohol, coagulated proteid will be found within the Bowman's capsules.

An explanation of the non-passage of fibrinogen is that its molecule is extremely large, much larger than that of serum globulin. This is indicated by its low coagulation temperature, ease of precipitation by salts, and proneness to change into fibrin, all facts suggestive of an extremely colloidal nature. It is, moreover, the least abundant of the proteids of plasma, though this will not completely explain its non-passage into the urine, for serum globulin is present in greater quantity than serum albumin, yet the albumin is more prone to pass than the globulin.

ALBUMOSURIA.—Occasionally proteoses (albumoses) are found in the urine; this was formerly termed peptonuria. Very rarely true peptone makes its appearance. Albumosuria is most frequent in conditions associated with pent-up pus—*e.g.* large abscesses, empyema, and purulent meningitis. It also occurs when there is liquefaction of inflammatory exudation, as in croupous pneumonia, and has been met with in septicæmia, typhoid fever, etc., in which case the proteoses are probably formed by the infective agents and excreted by the kidneys.

The proteose present in these cases is usually deutero-proteose, sometimes proto-proteose. True peptone has sometimes been detected in cases of pneumonia. Proteoses are also met with in the urine in a remarkable condition, which has been termed *myelopathic albumosuria,* associated with disease of bone—apparently sarcomatous (see Chap. XIX). The first case was described by Bence Jones in 1848, who recognised the curious nature of the proteid in the urine, which has been called, after him, "Bence Jones's albumin." The proteid in these cases has sometimes been hetero-proteose, though at others presenting characters of its own. On heating it is precipitated at about 60° C. (10°–15° lower than the coagulation temperature of serum albumin) but re-dissolves partially or completely on boiling, reappearing again on cooling, and hydrochloric or nitric acid throws down a precipitate which disappears on heating and reappears on cooling. This proteid has in some cases been found only in the urine and not in the tissues, but in others has been extracted from the bones.

HÆMATURIA AND HÆMOGLOBINURIA.—Blood makes its way into the urine in a number of diseases of the urino-genital tract:

(1) In disease of the kidney, particularly acute nephritis from any cause, chronic nephritis, long-continued congestion, thrombosis and embolism of the renal vessels, malignant disease, tuberculous disease, and calculus.

(2) In pyelitis.

(3) In acute cystitis, papilloma, tuberculosis, malignant disease, and calculus of the bladder, and in parasitic diseases, particularly bilharzia.

(4) In inflammation of the urethra, as in gonorrhœa.

(5) Rarely an aneurysm may rupture into the urinary tract.

The amount of blood varies much. In acute nephritis, renal thrombosis and embolism, malignant disease, and papillomata of the bladder it is frequently abundant; in the other conditions it is usually more or less scanty.

Blood, if present in small quantity, gives a peculiar smoky appearance to the urine; if in larger quantity, the urine becomes red, dark, or porter-coloured.

The blood may be recognised microscopically, which is the only way to distinguish it from blood-colouring matter, or by the guaiacum (guaiacum tincture and peroxide of hydrogen = blue) or spectroscopic tests.

In some instances it is the blood-colouring matter which is present. This is known as *hæmoglobinuria*, and occurs in any condition in which there is solution of blood-corpuscles, as in infective diseases, such as septicæmia and pyæmia, toxic conditions, such as poisoning with quinine, chlorate of potash, mineral acids, arseniuretted hydrogen, and snake-venom. It also occurs in Raynaud's disease and in the remarkable condition known as *paroxysmal hæmoglobinuria*, in which there are recurrent attacks of hæmoglobinuria from any slight cause—usually chill. The pathology of this condition is unknown, but the blood-corpuscles readily disintegrate, as may be shown by chilling the finger of the patient and examining the blood drawn from a prick; the serum will then be seen to be stained with hæmoglobin.

In some cases, as in black-water fever, the pigment in the urine is mainly *methæmoglobin*.

NUCLEOALBUMINURIA AND MUCIN.—As already stated, a trace of nucleo-proteid may be present in normal urine, and the quantity is sometimes increased. In inflammatory conditions a slimy deposit, generally referred to as mucin, is often present, which is regarded by Mörner as being a combination of proteid with chondroitin-sulphuric acid. In icterus, the urine sometimes gives a cloud with acetic acid, which disappears with excess of acid. This has been considered to be due to bile acids, but Parkes Weber[1] suggests that it is nucleo-proteid.

PYURIA.—Pus may appear in the urine in any inflammatory condition of the urino-genital tract, chiefly in pyelitis, cystitis, gonorrhœa, and tuberculous disease, or by rupture of an abscess into the tract, or from leucorrhœa. It is easily recognised by the microscope, is converted into a slimy mass by caustic potash, and urine containing it always contains proteid.

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[1] Discussion, Path. Soc. Lond., *loc cit.*

CHYLURIA AND LIPURIA.—A urine milky from the presence of fat, and containing proteid and usually fibrin, is met with in filariasis, and is known as *chyluria*. Fat in the urine (*lipuria*) may also occur in pregnancy, diabetes, and phosphorus poisoning.

HÆMATOPORPHYRINURIA.—A pigment, hæmatoporphyrin, present in traces in normal urine, is sometimes much increased in pathological conditions, and may give the urine a more or less red colour. It is especially found in sulphonal poisoning. It is an iron-free derivative of hæmatin and isomeric with bilirubin. It may be detected by Garrod's method: add to the urine one fifth of its volume of 10 per cent. caustic soda; this precipitates the phosphates which carry down the pigment. The precipitate is then extracted with alcohol acidified with hydrochloric acid and the solution examined spectroscopically. It shows a faint narrow band between C and D, and nearer D, and a darker broad band between D and E.

ALCAPTONURIA.—This is a condition in which homogentisic acid is passed in the urine. Attention is usually directed to it by brownish staining of the linen. Homogentisic acid is dioxyphenylacetic acid; it reduces alkaline copper solutions, but not alkaline bismuth solutions, and is non-fermentable. It gives a lemon-yellow colour with Millon's reagent, becoming brick-red on warming. Some seventy cases of this condition have been recorded. It seems to be present from birth, is always of about the same degree; *i. e.* allowing for age and quantity of food consumed, the amount of homogentisic acid excreted is approximately the same in all the cases. The amount varies with the kind of food, and it seems that aromatic bodies having two hydroxyl groups in the 2 : 5 positions in the ring cannot be properly broken down and assimilated, with the result that the acid appears in the urine, giving rise to alcaptonuria. The condition must be regarded as a congenital defect in normal metabolism; it is more or less hereditary, and tends to run in families, but is of no pathological import, the individuals the subject of the anomaly not suffering in any way.

BILE.—Both bile-acids and bile-pigments occur in the urine in cases of jaundice. In the slighter cases the urine may be merely orange in colour, but in intense cases it is dark, or even porter-coloured. It tends to stain the linen yellow, and any casts present will also be stained.

The bile-acids may be detected by Pettenkofer's test (cane-sugar + H_2SO_4), which, however, fails if the urine be dark, unless extraction be previously performed. Hay's test is a good one: flowers of sulphur sprinkled on the surface of normal urine float; in urine containing bile-acids they sink owing to a diminution in surface tension. On this physical character Otto Grünbaum has devised a method for estimating their amount.

Bile-pigment may be detected by Gmelin's test (fuming nitric acid) or by Smith's reaction (floating some tincture of iodine on the urine = green ring).

MELANIN.—In cases of melanotic sarcoma the urine frequently contains dark pigments, which have been termed "melanins."

LEUCIN AND TYROSIN.—These substances are found in the urine, especially in acute yellow atrophy of the liver and in phosphorus poisoning. If forming a sediment, they may be recognised microscopically (leucin forms spherical granules [Fig. 11, *a*], tyrosin sheaves or rosettes of needle-shaped crystals [Fig. 11, *b*]), but if in solution extraction must be performed.

Cystin, a sulphur-containing derivative of proteids, is occasionally met with in the urine (*cystinuria*), sometimes forming a deposit, or even a calculus. It does not seem to be connected with any definite pathological condition.

Cystin *per os* does not appear in the urine, but if injected into a peripheral vein cystinuria results, but not if injected into a mesenteric vein and passed through the liver; in the latter instance it seems to be converted into taurin.[1] Cystin crystallises in hexagonal tablets (Fig. 11, *g*).

Calculi of various kinds occur in any part of the urinary tract, but mainly in the pelvis of the kidney and in the bladder. To be present in the ureter and urethra they must be impacted, partly from their size, partly from the œdema and inflammation set up by their presence. Several calculi may be present in the pelvis of the kidney; in this situation they usually consist of uric acid (on calculi in the bladder see p. 447).

Glycuronic acid (or glucuronic acid) $C_6H_{10}O_7$, a derivative of dextrose, may occur in the urine, particularly as compound glycuronates, *e.g.* phenol, idoxyl, and skatoxyl glycuronates, after the administration of chloroform, chloral hydrate, camphor, turpentine, and morphine. Since glycuronic acid and some of the compound glycuronates reduce copper and bismuth, they are of importance in testing for sugar, from which they may be distinguished by the fermentation test; they are not fermented.

Medicinal substances.—Many alkaloids when administered pass into the urine—*e. g.* quinine, morphine, and strychnine. When turpentine, copaiba, or other resins are being taken they appear in the urine as resin acids. Rhubarb, senna, and particularly santonin, give a yellow or dark colour to the urine. Phenol gives a greenish colour (*carboluria*), due to derivatives of hydroquinone. Asparagus gives a characteristic odour to the urine, and turpentine an odour of violets.

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[1] See Simon and Campbell, *Johns Hopkins Hosp. Bull.*, November, 1904, p. 365.

REDUCING SUBSTANCES AND CARBOHYDRATES IN THE URINE.—Some of the reducing substances met with in the urine have already been mentioned—viz. uric acid, kreatinin, and glycuronic acid. By far the most important reducing substance is, however, *dextrose*, which occurs in glycosuria and diabetes mellitus (see p. 198). In the urine of pregnant women *lactose* may pass into the urine, but is difficult to distinguish from dextrose. *Lævulose* has been met with occasionally in diabetes, and *pentose* in the morphia habit and in pancreatic diabetes. *Inosite*, $C_6H_6(OH)_6.H_2O$, though having the simple formula of a carbohydrate, is really hexahydroxy-benzene, and occurs in diabetes insipidus (see p. 414). It does not reduce cupric hydrate, but keeps it in solution, gives negative reactions with Moore's and the bismuth tests, and is not fermentable by yeast.

Excretory Activity of the Kidney.

The *rôle* played by the various structures of the kidney in the elimination of the various constituents of the urine is still only in part elucidated. There is no experimental evidence of the existence of any special nerves, apart from the vasomotor ones, controlling the mechanism of excretion. There seems to be some correlation between the activity of the skin and of the kidney, but how this is brought about is uncertain.

It may be that some chemical agent, analogous to secretin in the case of the pancreas, influences the renal secretion but at present this is unknown.

It is generally admitted that the glomerulus is the part of the renal apparatus by which the *water* is excreted. Whether this excretion of water is a purely mechanical process of filtration, or whether the epithelial cells exert a secretory function in addition, is still debated; probably the latter view is correct. A point of interest is that all the ordinary constituents of the urine—urea, salts, etc.—have a diuretic action, and give rise to excretion of water, and, therefore, to their own elimination. The state of the circulation in the kidney profoundly influences the excretion of water. Anything which raises the blood-pressure increases, anything which reduces it diminishes, the excretion. Stimulation of the central end of most afferent nerves raises the blood-pressure generally, including that of the kidney, by vaso-constriction.[1] Stimulation of the central end of the depressor nerve similarly reduces the blood-pressure. Excitation of the central end of the lower dorsal and upper lumbar posterior roots causes reflexly engorgement of the kidney, owing to dilatation of the renal vessels. This effect is seen in shock, in which the secretion of urine is much diminished, or, for a time, in abeyance.

The amount of renal substance also has a marked influence on the quantity of urinary water, but the mode in which it acts is by no means clear. Removal of a portion of one kidney (simple incision is ineffective) in an animal is followed by a temporary increase in the volume of urine. If, in addition, the sound kidney is removed, the increase becomes permanent and may amount to from two to four times the normal, though it is unassociated with any cardio-vascular changes. It has been supposed by some that a portion of the water excreted by the glomerulus is reabsorbed as it passes down the tubules, and the action of some diuretics, such as caffeine and urea, might be supposed to consist in preventing re-absorption, and this theory would suggest an explanation of the experimental fact (which has a parallel in chronic interstitial nephritis) that when one third or one quarter only of the total kidney substance remains, the quantity of urine is increased. The reabsorption of water by the renal tubules, whether cortical or medullary, is, however, in no way proved at present, and the phenomenon recorded possibly depends on some reflex effect on the vascular system.

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[1] **For many suggestions in this section I am indebted to Dr. Rose Bradford's "Croonian Lectures," *Lancet*, 1904, vol. i, p. 125, *et seq*.**

With regard to the excretion of the other normal constituents of the urine, the question arises as to whether they are brought to the kidney as such, and simply *picked out* and eliminated by the renal epithelium, or whether they are *formed* by the epithelial cells from intermediate substances or precursors. In the case of urea and of uric acid the evidence is complete that they are formed elsewhere than in the kidney. Urea is normally present in small quantity in the blood to the extent of about 0·01 of the percentage present in the urine, but if the kidneys be extirpated it accumulates in large quantities in the organs, tissues, and blood. The same may be said of the other normal urinary constituents. The excretory function of the tubular epithelium may be shown by injecting into the blood-stream of an animal sodium sulphindigotate. This substance is rapidly eliminated by the kidneys and colours the urine blue; and if while this process is going on the animal be killed and the kidneys fixed in absolute alcohol, these organs will be found to be blue and the glomeruli are the only portions of them which are not coloured by the dye. The selective action of the renal epithelium is demonstrated by the fact that whereas five times as much sugar as urea is normally present in the blood, it is only the urea which is eliminated. On the other hand, that the renal epithelium has also a constructive power in certain instances is equally true. Thus, after the administration of benzoic acid, hippuric acid appears in the urine, and that it is formed by the activity of the renal epithelium is proved by the fact that if defibrinated blood containing benzoic acid and glycin be perfused through the kidney, hippuric acid is formed, and similarly if phlorizin be perfused, glucose appears in the urine.

A much debated point is whether the kidney possesses an internal secretion. The profound difference noticed between acute uræmia in the course of disease such as scarlatinal nephritis and the latent uræmia which occurs when both ureters are blocked from any cause has suggested that in the former case, the whole kidney being disorganised, the supposed internal secretion would be in abeyance, while in the latter, the renal structure being intact, the internal secretion still goes on, and hence the disturbance is much less and life more prolonged. A somewhat similar difference is noted between double nephrectomy and ligature of both ureters. Attempts have also been made to show that renal extract is of service in uræmia. The evidence is by no means favourable to this view, and the existence of an internal secretion cannot be said to have been demonstrated. Nor are there histologically any structures or groups of cells to be detected in the kidney which might be regarded as forming the internal secretion.

INCREASE OF THE URINARY SECRETION: POLYURIA.—An increase in the amount of the urinary secretion is frequently seen and is known as *polyuria.* A transient polyuria may be caused by:

(1) All causes which increase the general blood-pressure and coincidently the pressure in the renal artery.

(2) The entrance into the circulating blood of substances having high endosmotic equivalents, causing a passage of fluid from the tissues into the blood-vessels, with consequent increased volume of blood and increase of blood-pressure.

(3) Diuretic substances which stimulate the glomerular epithelium.

(4) Psychical emotions, as in hysteria (candidates undergoing the stress of examination frequently suffer from polyuria).

(5) Diminution of loss of water by the skin and lungs, as in cold weather, particularly when cold east winds prevail.

(6) Polyuria may be "critical," as at the crises in pneumonia or in ague.

In polyuria it is sometimes the water alone that is increased (*hydruria*); sometimes in addition the phosphates (*phosphaturia*) or the nitrogenous constituents and urea (*azoturia*) are in excess.

Diabetes mellitus is the commonest condition which clinically presents a marked polyuria.

Chronic renal disease, particularly that associated with the granular kidney, is frequently accompanied with an increased flow of urine, which has been attributed to the coexistent cardio-vascular lesions, particularly to the cardiac hypertrophy, and consequent increased arterial pressure, as evidenced by the high-tension pulse. But advanced renal disease may exist without associated cardio-vascular changes, and a copious watery urine still be secreted. This is well seen in lardaceous kidney, in some forms of hydronephrosis, in advanced cystic disease, and occasionally in contracted white kidney. Paradoxical as it may seem, it may be said, therefore, that renal disease, particularly if extensive, tends to increase rather than to diminish the flow of urine—a point of some clinical importance. In cases of renal disease in which the flow is diminished the diminution is probably dependent on some associated condition—active congestion, as in nephritis, passive congestion, as in heart-disease, increased loss of water by other channels, or the onset of dropsy.

Diabetes insipidus.—This is a rare disease, in which the volume of the urine is remarkably increased up to, it may be, ten times the normal, sugar, albumen, and renal changes being absent. It is usually a hydruria, but sometimes there is azoturia or phosphaturia. It occurs chiefly in young adults, and thirst (*polydipsia*) is a prominent symptom, and is probably primary. It has been ascribed to a persistent increase in the glomerular blood-pressure, due to vaso-motor disturbance, to changes in the blood, which alter its endosmotic power, to inosituria, the presence of inosite (see p. 409), which is occasionally met with, but by no means always, and to nerve-lesions. Diabetes insipidus has been met with in trauma and various diseases of the central nervous system, and it is possible to produce polyuria experimentally by various nerve-lesions, *e. g.*:

(1) Wounds of the floor of the fourth ventricle frequently.

(2) Cutting the greater splanchnics in dogs causes increased secretion of urine, which is inhibited by stimulating the peripheral cut end.

(3) Mechanical injury of the middle lobe of the cerebellum.

Persistent polyuria may be produced in rabbits by destruction of minute areas in the cerebellum and medulla.

DIMINUTION AND SUPPRESSION of the urinary secretion occurs from many causes—*e. g.* increased excretion of water by other channels, as by sweating and diarrhœa. In fever the volume of urine is diminished, partly on account of increased elimination by the skin, but partly, also, owing to diminished secretory activity of the kidney. Lowering of the general blood-pressure, such as occurs in shock, brings about diminution, or even suppression, of urine. In passive congestion, as in heart-disease, and active congestion in inflammation of the kidney, there is also lessened secretion, which may amount to complete suppression. Congestion probably acts by retardation of the blood-flow through the kidney and consequent fall of blood-pressure. Inflammation doubtless acts partly in the same way, and the blood and casts which block the tubules must add materially to the difficulty of secretion, though Cohnheim dissents from this latter view. The damage to the living excretory cells produced by the agent causing the inflammation must also be a factor inducing diminished activity. We are not yet, however, in a position completely to explain the action of inflammation in causing suppression of the urinary secretion. The passage of a catheter may also cause suppression, perhaps reflexly by vaso-motor impulses, but this is uncertain.

If the flow of urine be not soon re-established, the condition known as *uræmia* supervenes.

Suppression of urine is met with, therefore, chiefly in structural disease of the kidney. Another form, which may be termed "obstructive suppression," occurs usually when one ureter becomes blocked with a calculus, the other kidney being functionally inactive through disease, or congenitally absent. Rarely both ureters may be simultaneously blocked by calculi. Blocking of both renal arteries by emboli would also lead to suppression.

Uræmia is a toxæmia, arising usually in the course of acute or chronic renal disease, and is analogous to other toxic states, such as acetonæmia and cholæmia. Clinically, it may be acute or chronic, the chief symptoms being somnolence and coma, twitchings, transient blindness, and epileptiform convulsions, together with headache, gastric disturbance, dyspnœa, and Cheyne-Stokes' respiration. Acute uræmia is invariably preceded by suppression, or at least marked diminution, of the urine, and is generally associated with acute nephritis. Chronic uræmia is usually accompanied with some diminution in the amount of urine, and is associated with chronic nephritis. Latent uræmia is the condition which ensues on blocking of the ureters, or both renal arteries, double nephrectomy, etc., and presents a picture very different from that of acute and chronic uræmia, as will be described later.

The earliest theory to account for the uræmic symptoms was that of Traube, who ascribed the condition to œdema and anæmia of the brain, the result of heightened arterial tension, but this is not tenable.

Uræmia, acute or chronic, associated as it generally is with suppression or diminution of the urinary secretion, might be supposed to be due to the accumulation in the blood of some urinary constituent or constituents which are normally eliminated. It may be stated at once, however, that none of the urinary constituents—urea, uric acid, kreatinin, etc.—even when injected in large quantities, induces in the slightest degree a condition approaching that of uræmia. The only substances markedly toxic in urine are the potassium salts, and the uræmic symptoms are certainly not due to these. Uræmia also occasionally supervenes when there is little or no diminution of urine; though it is true that in such cases the quantity of urea and other urinary extractives is lessened, not necessarily to a great extent, but then such patients take very little food, not sufficient to produce the normal quantity of urea, etc. Moreover, as stated, abrogation of the functions of the kidneys by ligature of both ureters or by double nephrectomy, though the urinary constituents must accumulate, is not followed by acute uræmia. As previously stated, the urine is normally toxic, and Bouchard and others have shown that sometimes in uræmia the toxicity is diminished, indicating that toxic substances which should be eliminated are retained. But Rose Bradford states that even in the most acute uræmia the urine does not entirely lose its toxic action, and is often found to possess a toxicity quite comparable to that of the normal secretion. Bouchard claimed to have isolated toxic bodies, "urotoxins," from the urine, but their existence is doubtful (see below, p. 420).

Frerichs ascribed the condition to ammonium carbonate, into which he supposed the urea was converted by some ferment. Support was given to this theory by the ammoniacal odour of the breath, which is sometimes present, but this has been shown to be due to a local decomposition of nitrogenous matters in the mouth, and injections of ammonium carbonate do not induce uræmic symptoms. The blood in uræmia is diminished in alkalinity, and this has suggested that the condition is a manifestation of acid intoxication, but in all probability the diminished alkalinity is a result, and not the cause, of the uræmia.

Experiments performed to investigate the effect of throwing the liver out of the circulation by establishing a communication between the portal and hepatic veins (Eck's fistula) have shown that after this operation some of the symptoms of uræmia are produced. In dogs restlessness, convulsions, dyspnœa, depression, and coma may result, the attacks closely following the administration of proteid food, the urea in the urine is diminished, and ammonium carbamate is found in the blood. Now, ammonium carbamate ($CO.NH_2.ONH_4$) on heating is converted into urea, and is regarded as a precursor of urea:—

$$CO.NH_2.ONH_4 = CO.NH_2.NH_2 \text{ (urea) } + H_2O.$$

On these facts uræmia might be a carbamic acid intoxication.

Another fact which must be noted is that the general metabolism of the body is profoundly affected in renal disease, as evidenced by the wasting that is so marked a feature of almost all renal affections, a wasting quite out of proportion to the general symptoms. This is particularly seen in double nephrectomy, and it is possible that the kidney has some influence over nitrogenous metabolism. Brown-Séquard held that this influence was exerted by an internal secretion, but, as already stated, there is no definite evidence of the existence of such a secretion. It may be, therefore, that, owing to renal disease, abnormal tissue metabolism occurs, with the formation of toxic substances which, owing to the renal impairment, are not eliminated, and if these accumulate beyond a certain point uræmia results.

To sum up, uræmia must be regarded as a toxæmia, the result of auto-intoxication, the substances producing it being unknown; perhaps they are precursors of urea, but its exact pathology is still uncertain.

In uræmia, in addition to the usual renal and cardio-vascular changes of nephritis, the brain is frequently œdematous and hyperæmic, small hæmorrhages may be present in the brain and its membranes, and the ganglion cells are vacuolated and show chromatolysis. Œdema of the lungs is common, catarrh of the digestive tract is frequent, and degenerative changes of the myocardium and of glandular cells generally may be, and retinal changes are almost always, present.

The blood and fluids of the body are loaded with extractives, and the blood may contain 0·5 per cent. of urea instead of the normal 0·015 per cent. On the whole, the nitrogenous extractives tend in uræmia to be greater than in obstructive suppression.

Latent uræmia is the condition which ensues from obstructive suppression of urine when both ureters are blocked, or one ureter is blocked, the other kidney being disorganised or absent. Experimentally a similar, if not identical, condition may be brought about by ligature of both ureters, double nephrectomy, or blocking of both renal arteries. It differs essentially from uræmia, acute or chronic; the patient lives from a week to ten or eleven days; he has neither dropsy, vomiting, dyspnœa, nor convulsions, and is conscious to the last. He may be drowsy but is readily roused, and may show slight muscular twitchings, but the principal symptom is progressive asthenia, with fall in body temperature, and death usually results from sudden syncope. The pathology of the condition is uncertain, but it may legitimately be assumed to be due to the retention of the urinary constituents.

Puerperal eclampsia is another condition the pathology of which is uncertain. By many it is regarded as uræmic, but it is a question whether the renal changes and albuminuria are not secondary. In a small proportion of the cases renal changes and albuminuria are absent, which lends support to the latter view, and the affection may be a toxæmia dependent on abnormal or increased metabolism of the puerperal state. It has also been considered to be an infective condition.

TOXICITY OF THE URINE.—Bouchard and others have found the normal urine to be toxic when injected intravenously into rabbits, about 60 c.c. causing death. As the urine is injected, first the pupils begin to contract, the animal becomes drowsy, and a few muscular twitchings are observed. The rate of respiration then becomes slower, the animal rouses and becomes restless, convulsions and strong opisthotonos ensue, the eyes protrude, the pupils dilate, and the animal dies with subnormal temperature. Bouchard estimates that a healthy man weighing 60 kilograms will excrete in twenty-four hours sufficient urinary poison to kill 24 kilograms of rabbit, and it follows, therefore, that each kilogram of the man excretes enough to kill 0·4 kilogram of rabbit. The dose that is fatal to a kilogram of rabbit he terms a *urotoxy*, and the amount of poison excreted by each kilogram of body-weight *per diem* he calls the *urotoxic coefficient*. This varies under different conditions and in disease. Bouchard has further attempted to establish the existence of a number of "urotoxins," the sum total of which constitutes the toxicity of urine—viz. a narcotic substance, two convulsant substances, another which produces myosis, and a fifth which lowers the temperature, etc. Herringham,[1] after a careful survey of the facts and numerous analyses of urines, concludes that normal urine owes its toxicity to potassium salts alone, and that Bouchard's views are untenable. Doubtless in disease toxic substances may sometimes be excreted in the urine.

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[1] *Path. Soc. Trans.*, vol. l, 1899, p. 293.

Malformations and Displacements of the Kidneys.

COMPLETE ABSENCE of both kidneys is very rare, and is, of course, incompatible with life.

ABSENCE OF ONE KIDNEY, usually the left, is not infrequent. In such cases the remaining kidney is hypertrophied and the renal functions are unimpaired.

CONGENITAL SMALLNESS of one or both kidneys is sometimes observed.

FUSION OF THE KIDNEYS, more or less complete, is the commonest malformation. The organs are usually adherent by their lower ends and form a semicircular mass, the *horseshoe kidney,* which lies across the lumbar spine in front of the vessels, or may be placed in the hollow of the sacrum.

THE FETAL LOBULATION exists up to a year after birth, and may occasionally persist.

SUPERNUMERARY KIDNEYS, adherent to the normal ones, or lying free, are rarely observed.

DISPLACEMENT OF THE KIDNEY may be congenital or acquired. *Congenital malposition* is about twice more frequent in males than in females (*cf.* Acquired Malposition, below). The left kidney is more commonly affected than the right, and the displaced organ is usually permanently fixed in the abnormal condition.

ACQUIRED MALPOSITION is much more frequent in females than in males, is usually met with in young adults, and the right kidney is far more commonly affected than the left, probably because of the movements of the liver in respiration, which the right kidney follows, and also because the left kidney is anatomically more firmly fixed than its fellow. The affected kidney is also usually *movable,* or if extremely mobile, *floating.* The kidney is normally kept in place chiefly by the subperitoneal connective tissue on which it lies, and from some cause this becomes stretched, allowing of movement. The movable kidney either lies behind the peritoneum or invaginates this and acquires a mesonephron. The causes of the condition are obscure, and it has been ascribed to traumatism and strain, relaxation of the abdominal wall through pregnancy, displacement of the uterus, etc. It gives rise to discomfort, pain, and dragging, and pressure on other organs, and sometimes to more serious consequences, viz. kinking or torsion of the ureter, leading to hydronephrosis, intermittent or permanent (see also Glénard's disease, p. 337).

ENLARGEMENT OF THE KIDNEYS.—Congenital absence, disease, or removal of one kidney, is attended with a true or compensatory *hypertrophy* of the other. *Enlargement* of the kidneys occurs in many renal affections—congestion and inflammation, chronic parenchymatous nephritis, lardaceous disease, new growths, and cystic disease.

SMALLNESS OF THE KIDNEYS may be congenital or may be the result of disease, interstitial nephritis and arteriosclerosis, embolism, etc. In old age a *senile atrophy* frequently ensues.

Disturbances of the Renal Circulation.

ANÆMIA OF THE KIDNEY occurs in cases of general anæmia from any cause, and in pernicious anæmia, also in obstruction of the renal vessels by thrombosis or embolism or by pressure from without, tumours, bands, etc. It is also stated to occur as a result of vascular spasm, for example in hysteria, in epilepsy, and in strychnine poisoning. An anæmic kidney is pale and smaller and harder than normal. Microscopically, the principal change is fatty degeneration of the renal epithelium. Obstruction of the renal artery leads to complete necrosis. In anæmia the amount of urine is diminished, and albuminuria is frequently present owing to the degenerative changes.

Hyperæmia of the kidney may be active or passive. *Active hyperæmia* occurs in inflammation, also in conditions of increased arterial pressure in the aorta or renal arteries, and the latter gives rise to an increased secretion of urine.

Passive hyperæmia or congestion is principally met with in chronic cardiac and pulmonary diseases, particularly mitral regurgitation and stenosis, and emphysema. Obstruction of the renal veins or of the inferior vena cava may also cause it. The kidney becomes enlarged, darker in colour, and engorged with blood. Microscopically, the vessels are dilated, and hæmorrhages may be present in the interstitial tissue and within Bowman's capsule.

Degeneration of the tubular epithelium may be seen, the amount being dependent on the duration of the condition, and hyaline casts or cylinders, consisting of a solidified albuminous exudate, may be present in the lumen of the tubules. If a moderate degree of engorgement persists for any length of time, the condition known as *cyanotic induration* ensues, characterised by denseness of the renal tissues, paleness of the cortex, which is streaked with dark lines, the kidney itself being dark in colour and not materially enlarged or even being smaller than normal.

In passive congestion the urine is diminished in quantity, its specific gravity is increased, it may deposit urates and contain albumin and a few hyaline casts and blood-cells.

Hæmorrhages into the renal substance are generally small, usually derived from the glomerular vessels, and occur in congestion and inflammation. They may occur in the new-born as the result of difficult labour. More extensive hæmorrhage is the result of traumatism, thrombosis, or infarction. The blood may find its way into the pelvis and cause hæmaturia, or, if the capsule be ruptured, extravasate into the surrounding tissues, and may then be very extensive.

THROMBOSIS AND EMBOLISM.—Embolism is far more common than thrombosis, which is rare.

Thrombosis of the renal vein may occur as a result of compression by tumours, etc., by extension of inflammation from the kidney, or of thrombosis of the vena cava. It also occurs in infants the subjects of marasmus, and occasionally in infants shortly after birth, apparently from septic infection. The kidney is swollen, œdematous, and hæmorrhagic in this condition.

Thrombosis of the renal artery is rare, and occurs as a result of arterial disease or extension of the clot from an abdominal aneurysm.

Embolism is not uncommon, and, the renal arteries being "terminal," usually gives rise to infarction. It arises from separation of vegetations in endocarditis, simple or infective, and in atheroma, with polypoid thrombi or aneurysmal clots of the aorta. The immediate result of the stoppage of the circulation is anæmia of the affected part, which assumes a yellowish or greyish tint. After a few hours more or less hyperæmia of the part ensues, together with hæmorrhage by diapedesis, mainly from the intertubular capillaries. The amount of hæmorrhage varies; sometimes it is slight and limited (non-hæmorrhagic infarct), or it may be extensive (hæmorrhagic infarct), in which case the involved area becomes dark red. This, however, soon changes, and in two or three days the blood-colouring matter becomes absorbed, and the patch pale once more. The changes which occur are death and degeneration of the epithelium, and disintegration of it and of the other tissue elements, the glomeruli persisting longest; but these too ultimately undergo conversion into colourless spherules. Eventually new vessels penetrate the part, which finally becomes converted into a patch of fibrous tissue, with contraction and puckering. Macroscopically, an infarct appears as a pale, wedge-shaped area, with its base at the periphery, its size depending on the size of the obstructed artery, and varying from 1 mm. to 4—10 mm. at the base. If the infarctions be numerous and large, as may happen, the subsequent contraction of the cicatrices may give rise to a small, irregular kidney, *the embolic contracted kidney.*

Complete restoration of the embolised region can hardly occur, since the renal epithelium dies within about two hours after deprivation of its blood-supply. Clinically, embolic infarction is accompanied with hæmaturia, and may superficially simulate acute Bright's disease.

Infiltrations and Degenerations.

INFILTRATION WITH CALCAREOUS SALTS, *calcium phosphate* and *carbonate,* is met with in old age and in cases in which absorption of bone is taking place; occasionally, also, in interstitial inflammation. The deposit may be microscopic in the form of grains, or may form visible greyish striæ in the medullary zone. *Triple phosphate* may also occur when the urine is alkaline from decomposition. *Calcium oxalate* may be deposited in cases in which the food contains much oxalic acid or metabolic disturbance favours the formation of this acid.

URATIC INFILTRATION, in the form of uric acid, or usually of urate of sodium, occurs in the so-called uric acid diathesis. It forms whitish striæ both in the cortex and in the medulla. In new-born infants the condition is very common and has been ascribed to the rapid metabolic changes that ensue after birth. *Cystin*, *xanthin*, and *indigo* have also been met with.

Argyrosis, silver staining, occurs in the form of fine granules in the cortex after long administration of silver salts.

Biliary pigmentation occurs in jaundice. The pigment is seen as fine, yellowish, amorphous granules in the epithelium of the convoluted tubules. Rhombic, reddish crystals of *bilirubin* may be met with in icterus neonatorum.

Blood-pigments, hæmoglobin, methæmoglobin, and hæmatoidin, are met with in a variety of conditions, particularly poisoning with arseniuretted hydrogen, potassium chlorate, carbolic acid, and aniline compounds, in malaria and septic infection, after extensive burns, in paroxysmal hæmoglobinuria, after transfusion of blood of another species of animal, and after hæmorrhage into the kidney. The kidney may be enlarged and reddish-brown in colour, and the pigment is seen as brownish granules, or sometimes crystals, particularly in the tubules.

Bacteria may occur in the glomeruli, or as casts in the tubules, in pyæmia, anthrax, typhoid fever, etc.

Glycogenic infiltration occurs in diabetes, the glycogen forming glistening granules, particularly in Henle's loops.

Leukæmic infiltration in leukæmia is characterised by an accumulation of leucocytes in the interstitial tissue. The kidney may be much enlarged, pale, or mottled with greyish areas.

Lardaceous infiltration, the lardaceous kidney, frequently accompanies lardaceous change elsewhere and results from prolonged suppuration, particularly when tuberculous, and syphilis, also in advanced chronic inflammation (see p. 436). The condition principally affects the glomeruli, first appearing as waxy flakes in the subendothelial connective tissue, but later the whole tuft may be converted into a waxy sphere. In advanced cases the greater part of the capillary and venous systems of the cortex may be affected, and even the membrana propria of the tubules (Fig. 1, p. 24). Fatty degeneration of the whole renal epithelium frequently accompanies the lardaceous change. The tubules may contain fatty detritus, or casts, and waxy cylinders (? lardaceous or hyaline). A lardaceous kidney is much enlarged, pale and translucent or mottled, dense, and tough. The capsule is thickened and usually strips easily, leaving a smooth surface; occasionally it is slightly adherent. Iodine and gentian violet give the lardaceous reactions. The urine is generally increased in quantity and of lessened specific gravity, and contains much albumin and a few hyaline casts. When there is much fatty degeneration as well, the urine may be diminished and contain casts of all kinds.

HYALINE DEGENERATION may precede lardaceous change or may accompany interstitial nephritis. It chiefly affects the glomeruli.

CLOUDY SWELLING, or degeneration, affects the epithelium of the tubules. The affected cells become swollen, irregular, and elongated, granular, and lose their striæ and finally their nuclei, and fat globules may make their appearance (Fig. 2, p. 29). The kidney may be slightly enlarged and paler than normal. The condition is especially met with in infective diseases—diphtheria, scarlatina, typhoid fever, etc., also in phosphorus and other poisoning.

Dropsical degeneration occurs in general dropsy and in inflammation, and affects the glomerular and tubular epithelium.

Fatty degeneration.—Fatty change is a frequent accompaniment of renal infiltrations and degenerations, as already mentioned. It also occurs in acute inflammation, anæmia, infective diseases, and poisoning with phosphorus, arsenic, chromic acid, etc.

Extreme fatty change is seen in chronic parenchymatous nephritis. The renal epithelium, particularly of the tubules, is the chief seat of the change, but it may involve the vascular endothelium and the connective tissue, and be localised or diffuse. The organ is enlarged, pale or yellow, and the cortex widened.

Casts.—When there is albuminuria the proteid may coagulate and form *hyaline casts* in the tubules, which may also contain in the various renal affections *epithelial, fatty, granular,* and *waxy* casts, as the case may be.

Inflammation of the Kidney—Nephritis and Bright's Disease.

The subject of renal inflammation is a difficult one, both clinically and pathologically. It was in the early part of the last century that Richard Bright clearly proved and enunciated the connexion between dropsy, albuminuria, and disease of the kidney, and since his time this combination has clinically been known as "Bright's disease." More recently many authorities have regarded "nephritis" and "Bright's disease" as synonymous terms, and have therefore advocated the disuse of the latter one. But it seems convenient to retain "Bright's disease" as a clinical term for non-suppurative inflammatory renal affections accompanied with gross structural change and associated with albuminuria and dropsy. This limitation would exclude febrile albuminuria, the slight transitory nephritis so common in the course of febrile diseases, lardaceous disease which is non-inflammatory, and the arteriosclerotic kidney in which albuminuria is slight or frequently absent and dropsy, if it occurs, is of cardiac origin.

From the pathological standpoint Bright's disease may be considered under Nephritis, and will be so treated here.

Nephritis may be acute or chronic, parenchymatous, diffuse, or interstitial, non-suppurative or suppurative.

With regard to the ætiology of Bright's disease it may be stated at once that it has been impossible experimentally to produce a condition at all like that met with clinically. Although in Bright's disease the kidney is structurally altered, the disease is not simply one of this organ but is more widespread and must be regarded as due to the circulation of some toxic substance which has a marked effect on the renal structures and by its action on the vessel-walls induces dropsy. The action of a toxin in producing dropsy is well seen in beri-beri, in which the kidney is but little, if at all, affected, albuminuria is absent, and yet the anasarca and dropsy may be as pronounced as in any case of acute Bright's disease and has a similar distribution. It must be admitted, however, that no substance having this property of inducing dropsy has been isolated in nephritis. The condition is met with chiefly as a result of chill and in the course of infective diseases, particularly scarlatina and diphtheria. Chill probably acts as an exciting cause, as in pneumonia, rather than as a *causa causans.*

Many substances are capable of producing structural change in the kidney, and have been divided by Lindmann into three groups. Cantharidin produces intense glomerular changes, metallic salts and oxides of the heavy metals (lead, mercury, etc.), chromic acid and bichromates produce a coagulative process in the epithelium of the convoluted tubules, with disappearance of the nuclei and necrosis, while a number of organic poisons, snake-venom, abrin and ricin, eel-serum, etc., while attacking the renal epithelium, do not produce the disappearance of nuclei and necrosis which is characteristic of the metallic poisons. Vinylamine, a primary amine of vinylic alcohol, is also a marked renal poison attacking the glomeruli and epithelium of the convoluted tubules, but not that of the straight tubes.

None of these substances, however, when administered experimentally induces the dropsy and acute uræmia which so frequently accompany acute nephritis.

Nephritis which is due to substances circulating in the blood is termed "*hæmatogenous.*"

The term *parenchymatous* is applied when the changes are most marked in, and mainly limited to, the glomeruli and tubules, *diffuse* when the interstitial connective tissue is affected in addition, and *interstitial* when exudation, and especially proliferation, are conspicuous in the interstitial connective tissue, the other lesions being mainly secondary to this condition.

The classification of nephritis is an extremely difficult subject; every authority gives a different one, and some of the schemes proposed are very intricate.[1] The division of the subject here adopted is a convenient one, and includes all the main varieties without being needlessly complex.

Acute Nephritis.

ACUTE DIFFUSE NEPHRITIS is the ordinary form of acute Bright's disease following chill, and occurs in various infective diseases—*e. g.* diphtheria and scarlatina, and after poisoning with various substances such as carbolic acid, cantharides, and chromic acid. In the early stages the kidney is enlarged, deep red in colour, contains much blood, but later may be pale, or yellowish, or mottled, owing to degenerative changes and anæmia from pressure of inflammatory exudation and epithelial swelling. The cortex is increased in thickness, punctate or linear hæmorrhages may be present in intense cases, and the capsule strips easily, leaving a smooth surface. There is considerable sero-fibrinous exudation into the substance of the kidney. Microscopically, the glomeruli in some cases may not be much affected; generally there is swelling and desquamation of the epithelium. It is upon the epithelium of the tubules, both in the cortex and medulla, that the stress of the disease mainly falls. The epithelial cells are everywhere swollen and loosened, and in many places detached, and if the disease has lasted any time they become granular, fatty, and disintegrated. The lumen of the tubules is first empty, but subsequently becomes filled with hyaline casts and granular and fatty epithelial detritus. In the severer types hæmorrhages are seen in the glomeruli, tubules, and stroma. The stroma is swollen and infiltrated with a coagulable exudation containing a few cells, with here and there a patch of cellular infiltration.

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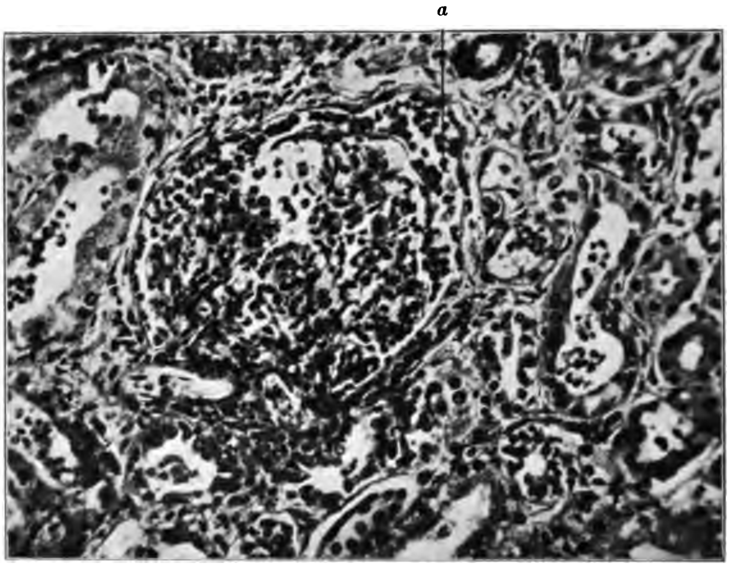
[1] See Zeigler's *Text-Book of Pathological Anatomy and Pathogenesis*, and Councilman, *Med. and Surg. Rep. of the Boston City Hospital*, 1897.

ACUTE GLOMERULAR NEPHRITIS.—The glomeruli are sometimes mainly affected; this is particularly the case in scarlatina, but may occur in any infective process. The naked-eye appearance of the kidney is not usually altered to any sensible extent. In some instances there may be no marked histological change, merely a fibrinous exudation within Bowman's capsule, which coagulates by alcohol or by heat, forming a hyaline areola around the glomerular vessels (*adhesive glomeru-*

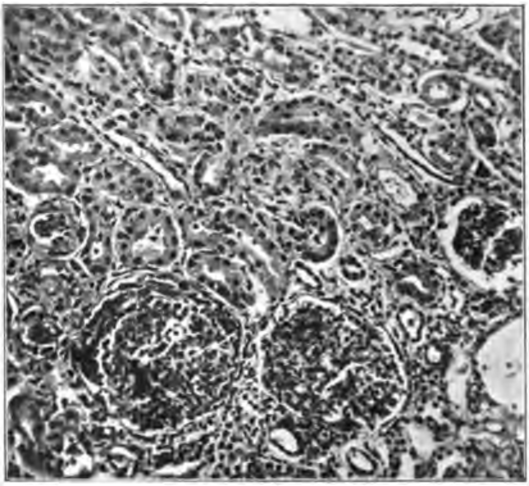
litis). This may subsequently become organised and obliterate the capsule. Usually there is some proliferation of the capillary endothelial cells of the glomerular vessels (*intra-capillary glomerulitis*) and proliferative and degenerative changes in the epithelium lining Bowman's capsule (*desquamative glomerulitis* (Pl. XVII., A.). The capillaries are dilated and crowded with large, nucleated, flattened cells, with a few polymorphonuclear leucocytes and chromocytes, and hyaline thrombi may be present in the vessels. The epithelial cells of both layers of Bowman's capsule may be increased in number owing to proliferation, or may be scanty, having become detached and washed away by the flow of urine. A few leucocytes and, in severe cases, hæmorrhages may also be present within the capsule. The desquamated epithelium undergoes granular and fatty degeneration. The tubules in some cases are almost unaffected (Pl. XVII., B.); in others, epithelial cells here and there are degenerate or necrotic, and hyaline casts may occupy the lumina. The intertubular connective tissue is generally quite unaffected, but occasionally may be slightly infiltrated with inflammatory exudation containing a few cells.

ACUTE INTERSTITIAL NEPHRITIS.—Sometimes the interstitial changes are much more marked than the parenchymatous ones, which may be largely secondary, and the condition is then designated an *interstitial nephritis*. It may occur in the course of any infective disease, especially in childhood, and was found by Councilman in 24 out of 103 cases of diphtheria, and in 5 out of 20 cases of scarlatina. The kidney is normal in size, or but slightly enlarged, and there is often little naked-eye change to be observed. The capsule strips easily, and in pronounced cases when degeneration has ensued the surface may be mottled with greyish patches. On

PLATE XVII.



A. Glomerular nephritis (scarlatinal kidney) showing multiplication of nuclei and exudation (*a*) in a glomerulus under Bowman's capsule. (Hæmatoxylin and eosin, × 120.)



B. Glomerular nephritis (scarlatinal kidney). Same section as A, showing that the tubules are comparatively unaffected. (Hæmatoxylin and eosin, × 75.)

section, the cortex is noticed to be increased to two or three times the normal, small hæmorrhagic patches may be present, and the renal tissue is soft and friable. Microscopically, a cellular infiltration is present, particularly at the base of the pyramids in the boundary between cortex and medulla and in the superficial region of the cortex around the stellate veins. Any glomeruli which lie in the affected areas may be surrounded with a dense cellular infiltration. The cells consist largely of plasma-cells, with polymorphonuclear leucocytes, some lymphocytes, and a few chromocytes, with here and there larger hæmorrhages. The glomeruli and tubules are as a rule but little affected; in some instances the tubular epithelium is cloudy or hyaline, and the tubules may contain some hyaline and leucocytic casts.

Suppurative nephritis occurs as a result of systemic bacterial invasion, or is secondary to pyelitis (*pyelonephritis*), or perinephritis. It may be met with in pyæmia, infective endocarditis, osteomyelitis, pneumonia, and other infective diseases. The bacteria may be carried to the kidney in the blood-stream as infective emboli (*embolic suppurative nephritis*), or may be free and simply lodge in the kidney. Both kidneys are usually involved, they are enlarged, and numerous, yellowish-white nodules are scattered through their substance. Microscopically, the changes are chiefly seen in the neighbourhood of the Malpighian bodies, which is invaded with dense collections of polymorphonuclear leucocytes. There is always degeneration and necrosis of the tissues in the vicinity. If the interstitial connective tissue breaks down, a *renal abscess* is the result.

Suppurative pyelonephritis occurs in ascending inflammation of the urinary tract secondary to cystitis, ureteritis, and pyelitis, the result chiefly of calculus or consequent on enlarged prostate (see also p. 442).

Perinephritis, inflammation of the tissue surrounding the kidney, occurs as an extension of inflammation from the kidney or from neighbouring tissues. If suppuration takes place, the condition is known as a *perinephritic abscess.*[1]

THE KIDNEY IN PREGNANCY.—Any form of nephritis may of course occur during pregnancy. The kidney is, however, occasionally involved in a peculiar manner, especially in primiparæ, which may lead to eclampsia, and the nature of which is disputed. By some it is regarded as a true inflammation, by others as a degenerative process due to auto-intoxication or to pressure. The changes are chiefly present in the glomeruli and tubules.

Chronic Nephritis.

Chronic nephritis presents many variations, but the main characteristics are either a diffuse inflammation with marked epithelial changes or interstitial hyperplasia of so great an extent as to overshadow the epithelial changes. We may thus distinguish a *chronic parenchymatous* and a *chronic interstitial nephritis.*

CHRONIC PARENCHYMATOUS NEPHRITIS, tubular nephritis, or chronic diffuse nephritis without induration, is usually the result of acute nephritis, but may also be chronic from the first. In the latter the ætiology is uncertain, but syphilis, alcoholism, and repeated exposure to cold and wet probably play a part. The kidney is usually enlarged, sometimes to twice the normal, and its consist-

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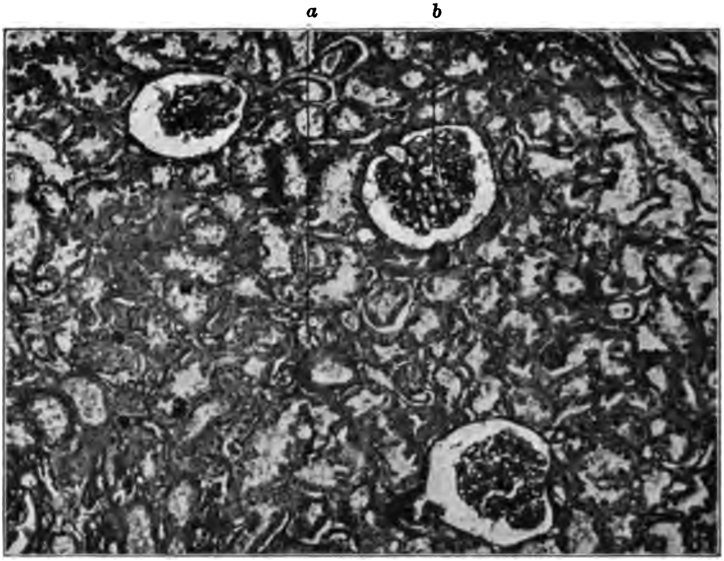
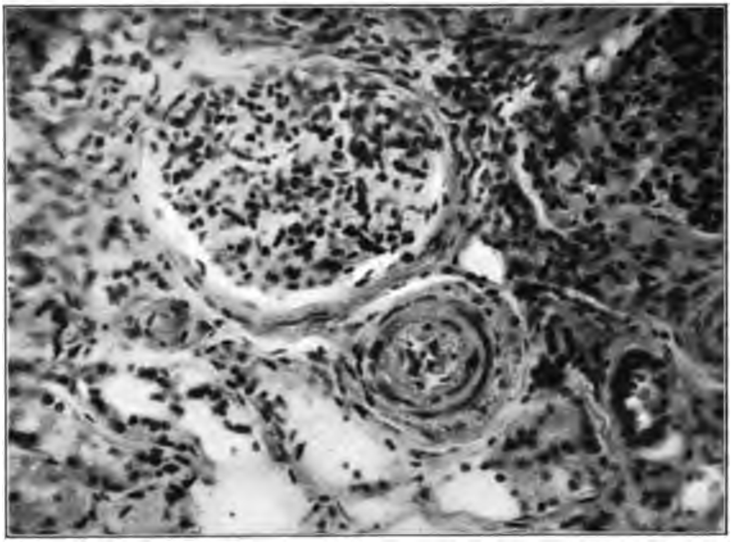
[1] The term *perinephritis* is sometimes limited to inflammation of the renal capsule, *paranephritis* being used to denote inflammation of the fibro-fatty tissue in which the kidney is imbedded.

PLATE XVIII.



A. Chronic parenchymatous nephritis, showing degeneration of the tubules (*a*), the glomeruli (*b*) being comparatively unaffected. (Hæmatoxylin and eosin, × 85.)



B. Chronic interstitial nephritis, showing thickening of Bowman's capsule and of a vessel. (Hæmatoxylin and eosin, × 120.)

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ence is diminished. The capsule strips easily, leaving a smooth surface. The cortex is increased in width, and is yellowish or mottled, the medullary pyramids are darker, and the cut surface has an oily feel, and oil droplets may be seen in a scraping. The colour varies; sometimes it is decidedly yellowish from the presence of fatty change and absence of blood (*the large white kidney*).

In other cases, owing to congestion and hæmorrhage, the kidney may be mottled in appearance (*mottled kidney*), it may not be much enlarged, and here and there the capsule may be adherent. As time goes on interstitial changes may predominate, leading to contraction, the *fatty contracted kidney*, or *secondary interstitial nephritis.*

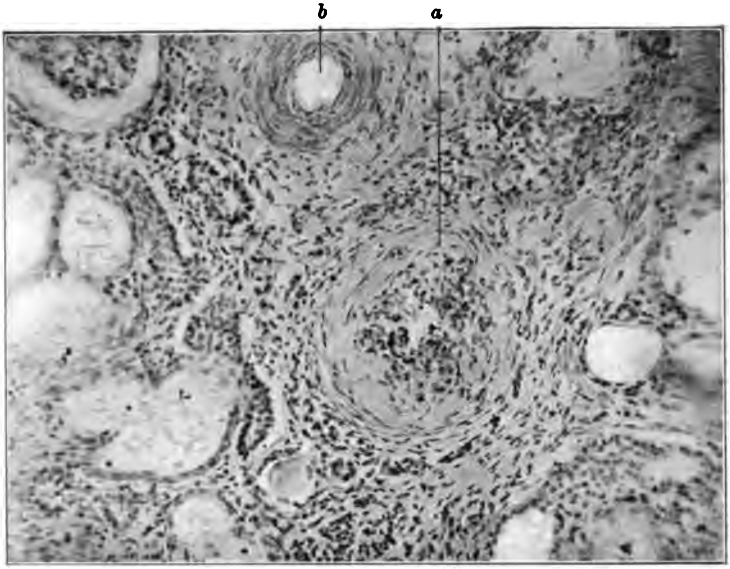
Microscopically, both degenerative and proliferative changes are seen. The tubular epithelium is always more or less affected, showing signs of cloudy swelling, fatty degeneration, desquamation and disintegration, most marked in the convoluted tubules, but also present in the loops and collecting tubes. The lumina of the tubes may be dilated, and contain granular and fatty matters and hyaline casts, the latter formed by coagulation of exudation in the tubules (Plate XVIII., A.). The glomeruli may occasionally appear normal, but there is almost always some swelling and hyaline degeneration, and, in addition, some proliferation and desquamation of the epithelium, so that they become highly cellular. Occasionally the glomerular changes may be more marked than the tubular (*chronic glomerular nephritis*). Interstitial changes, though present, are not conspicuous, and consist of œdema, and scattered foci of round-celled infiltration about the glomeruli and veins. Sometimes hæmorrhages are evident in some of the glomeruli and the corresponding tubules (*mottled kidney*).

Lardaceous infiltration frequently accompanies parenchymatous nephritis (*lardaceous large white kidney*).

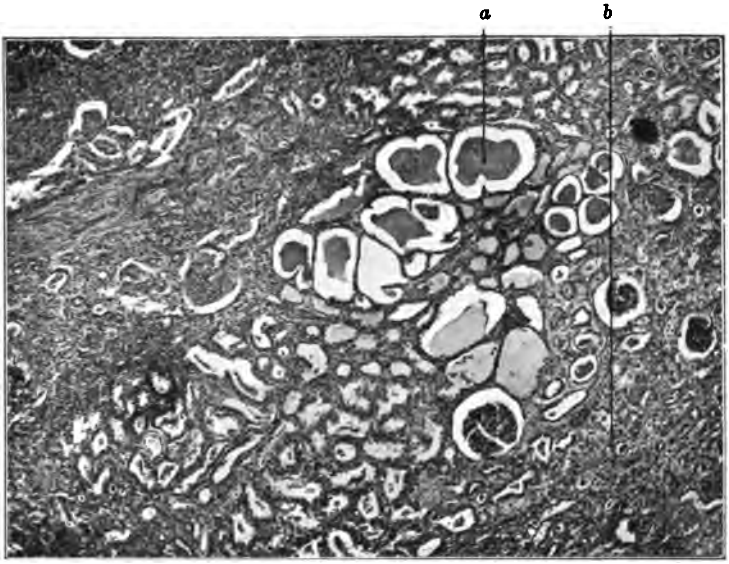
CHRONIC INTERSTITIAL NEPHRITIS, or chronic indurative nephritis, as mentioned above, may sometimes be secondary to chronic parenchymatous nephritis, connective-tissue overgrowth having become marked, and resulting in contraction of the kidney. Usually, however, it is a primary affection, and is known as renal cirrhosis, red granular, granular, or contracted kidney. The ætiology is obscure; probably some mild irritant acting for a long period is the cause, such as alcohol, the gouty poison, lead, and syphilis. Localised interstitial changes follow the healing of wounds or resolution of abscesses, infarcts, and gummata.

In the diffuse form the kidney is reduced in size, it may be to one third the normal or less, is hard and markedly granular. The capsule is adherent, leaving a rough surface on removal. Small cysts are often present on the surface filled with urine or colloid. The kidney is hard on section, the cortex much reduced in width, and cysts may be scattered through its substance. The colour is reddish with whitish mottling, and in gouty cases there may be whitish striæ, due to deposits of urate of soda. Microscopically, the lesions are principally seen in the cortex; there is great increase in the interstitial connective tissue, with destruction of glomeruli and the corresponding tubules. Bowman's capsules may be much thickened (Plate XVIII., B.), and the Malpighian bodies in places may be converted into nodules of fibrous tissue (Plate XIX., A.), in others into cysts (Plate XIX., B.). The corresponding tubules undergo atrophy with disintegration of their epithelium; here and there there may be multiplication, with convolution of the tubules, suggestive of an adenomatous formation. There is an increase everywhere of

PLATE XIX.



A. Chronic interstitial nephritis, showing a Malpighian body (*a*) almost converted into a fibrous nodule, and a vessel (*b*) much thickened. (Hæmatoxylin and eosin, × 75.)



B. Chronic interstitial nephritis, showing cystic dilatation of Malpighian body (*a*) and increase in fibrous stroma (*b*). (Hæmatoxylin and eosin, × 45.)

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the stroma, in the cortex and pyramids, between the tubules, and around the glomeruli and vessels (Plate XX., A.), with pronounced round-celled infiltration or well-formed fibrous tissue, in which calcification may occur. The vessel walls are thickened, chiefly owing to an endarteritis (Plates XVIII., B., and XIX., A.). Lardaceous infiltration may accompany the interstitial nephritis (*lardaceous contracted kidney*).

The *arterio-sclerotic kidney* is histologically much the same as the preceding, but in its early and primary form the vessels are mainly involved, the stroma being but little affected.

General Disturbance resulting from Nephritis.

URINE.—In acute nephritis the urine is much diminished in quantity and of high specific gravity, and is frequently suppressed. In chronic parenchymatous nephritis it is also diminished, but in interstitial nephritis it is increased in amount unless there is coincident congestion. In acute diffuse nephritis it contains much albumin and blood, and a sediment of blood, blood and epithelial casts, leucocytes and detached epithelial cells. In glomerulo-nephritis leucocytic casts are stated to be common. In chronic parenchymatous nephritis a large amount of albumin is present, the specific gravity is increased, and epithelial, granular, hyaline, and fatty casts are numerous. In chronic interstitial nephritis albumin is small in amount and frequently absent, especially in the morning, the specific gravity is lessened, and sediment is scanty, containing a few hyaline and granular casts. The freezing point of the urine is raised in nephritis, and the permeability of the kidney to methylene blue is altered; it is diminished in the granular kidney, increased in the large white kidney. In chronic nephritis the nitrogenous metabolism is lessened and the urinary nitrogen diminished. In acute and in chronic parenchymatous nephritis there may be considerable diminution in the gastric hydrochloric acid, with digestive disturbance, loss of appetite, vomiting, and diarrhœa.

Cardio-vascular changes are prominent. Irregularity and alteration in rhythm of the heart are common, and the arterial tension is increased, especially in the granular kidney. Dilatation and hypertrophy of the heart, particularly of the left ventricle, and most marked in granular kidney, are frequent. The cause of this has been much discussed; it is usually ascribed to the presence in the blood of substances which act as vaso-constrictors, thereby raising the blood pressure and increasing the peripheral resistance, to overcome which the heart undergoes compensatory hypertrophy. It is also stated that the viscosity of the blood is increased, which would tend to induce cardiac hypertrophy. There is anæmia in all forms of nephritis, the chromocytes and hæmoglobin both being reduced, the latter proportionately more than the chromocytes, but the leucocytes are unaffected. The blood is hydræmic, its specific gravity being reduced to 1030 or less, and contains more urea than normal, as well as toxic substances, while its freezing-point is reduced. Œdema and dropsy are very common, and the serous membranes are prone to be attacked by inflammation, *e. g.* pericarditis and pleurisy. Dyspnœa and Cheyne-Stokes' breathing are common in uræmia, an ammoniacal odour may be present in the breath, and bronchitis, pneumonia, œdema of the glottis and lungs, and hydrothorax are frequent. Headache, aphasia, and hemiplegia occur, cerebral hæmorrhage is a frequent event in granular kidney, and convulsions and coma are a part of the uræmic state. Retinal hæmorrhages, retinitis, and papillitis may be met with in all forms of Bright's disease, but are commonest in the granular kidney. Eczema and other skin eruptions have been described, the secretion of sweat is diminished, and the skin is often dry and branny. Fever is present in acute and subacute nephritis, rarely in uræmia.

TUBERCULOSIS OF THE KIDNEY is not infrequent. The miliary form is the commonest and occurs as a part of general miliary tuberculosis, but in chronic phthisis a few miliary tubercles are often present; they are most abundant in the cortex. Chronic localised tuberculosis also occurs, and is then usually an extension from uro-genital tuberculosis lower down, *e.g.* in the epididymis or bladder. In such cases the kidney may be enlarged, and on section presents one or more tuberculous centres, caseous or suppurating, which may attain a large size and the whole organ may be converted into a bag of pus. The inflammation frequently extends into the peri- and para-nephritic tissues. Both kidneys may be affected, but it is common to find the process much more advanced on one side than on the other. The pelvis is often involved, and the ureter may be attacked and converted into a gristly cord.

SYPHILIS OF THE KIDNEY in the form of gummata is uncommon, the syphilitic kidney being usually of the granular type with marked vascular endarteritis.

Actinomycosis and *leprosy* rarely affect the kidney.

Renal Tumours.

Benign tumours of the kidney are rare, usually small, and of little importance.

FIBROMATA may occur as small whitish growths the size of a pinhead to a pea, but occasionally they may be very large.

FIBROMYOMATA, consisting of fibrous tissue with both striped and unstriped muscle, and *lipomata* have also been observed.

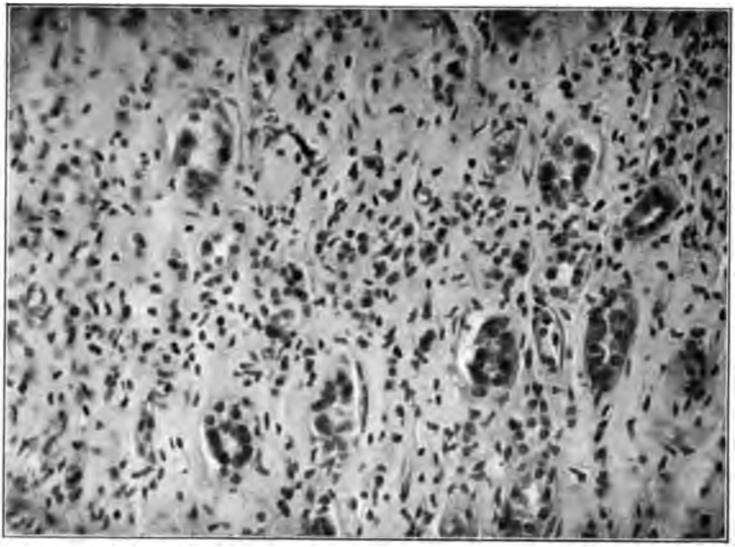
ADENOMATA are common in the granular kidney. They are generally small and caused by proliferation of the tubules.

SARCOMA is perhaps the commonest renal tumour; appears principally in childhood, may be congenital, and sometimes attains a very large size. Sarcoma of simple structure, *e. g.* round or spindle-celled, is the exception, the tumour generally presenting a curious admixture of sarcomatous elements with glandular tissue, striped and unstriped muscle, and even cartilage.

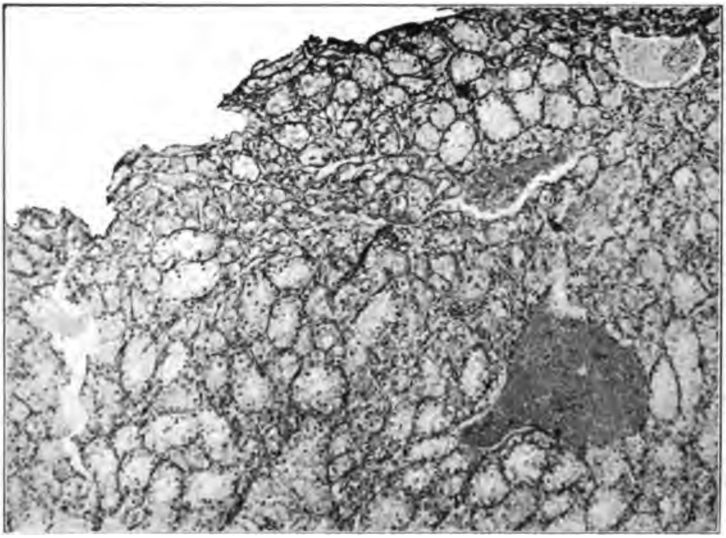
The histogenesis of these mixed tumours is obscure; some should probably be classed with the hypernephromata, derived from adrenal rests (see below), others may be derived from remains or rests of the Wolffian bodies or other embryonal structures.

HYPERNEPHROMA.—This is another remarkable form of renal tumour presenting wide variations in structure, and variously designated as carcinoma, endothelioma, and angeio-sarcoma. It is probably derived from inclusions of adrenal gland-tissue, is generally malignant, and met with after middle life, and varies in size, often being very large. In structure it consists of a stroma composed of a capillary network, the meshes of which enclose large round or polygonal cells containing well-marked nuclei; occasionally giant or multi-nuclear cells may be present (Plate XX., B.). Sometimes the cells are arranged in rows producing a resemblance to a tubular adenoma, or they may be columnar and grow in papillary masses into the spaces of the capillary network. Cysts are rare, but some portions of the tumour may be quite degenerate and friable, and show little or no structure.

PLATE XX.



A. Chronic interstitial nephritis, showing the increase in the fibrous stroma and obliteration of the tubules. (Hæmatoxylin and eosin, × 120.)



B. Hypernephroma of kidney. (Hæmatoxylin and eosin, × 55.)

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If the adrenals be derived from the pro- or mesonephros the hypernephroma must be classed as a carcinoma.[1]

Carcinoma is rare as a primary growth, and is then usually of the adenomatous type. Secondary cancer may occur in the kidney as in other organs.

Cysts are frequent, and small and multiple ones are common in the granular kidney. Now and then a single cyst or several large cysts may occur in a kidney otherwise healthy, and may be very tense and project from the surface. They may be congenital or acquired and probably depend on the blocking of some of the tubules.

Cystic disease of the kidney is usually congenital. The kidneys are enlarged and converted into a mass of smallish cysts. The condition may remain latent for a period and then give rise to sudden and fatal uræmia. Its causation is obscure, but has been ascribed to inflammation of the papillæ leading to atresia of the ducts. It may be met with in several members of a family, and be associated with cystic disease of the liver and pancreas. In hydronephrosis (p. 442) the kidney is converted into a large cyst. Dermoid cysts are very rare.

Animal parasites. Of these the echinococcus (hydatid) is the only one likely to be met with, and may form cysts from the size of a nut to that of a cocoanut. *Cysticercus cellulosæ,* filaria, and bilharzia may occur.

The Pelvis, Ureter, and Bladder.

The pelvis and ureter are subject to various malformations, they may be absent, rudimentary, or sometimes double.

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[1] See **Buxton,** *Journ. of Pathol. and Bact.,* vii, 1901, p. 221.

HYDRONEPHROSIS.—When the escape of urine from the pelvis is obstructed, dilatation of its cavity ensues. The obstruction is usually a calculus impacted in the ureter, but may be caused by blood-clot, parasites, or portions of a tumour, by pressure on the ureter from without, *e.g.* by a tumour or displaced uterus, or possibly by a fold of hypertrophied mucous membrane at the entrance of the ureter into the bladder. Sometimes there is a congenital stricture of the ureter. When the obstruction is complete moderate dilatation is the result, as the secretion of urine becomes suppressed, but if, after a time, the pressure of the accumulated urine is sufficient to overcome the obstruction, or if this be intermittent, the pelvis and calices may become enormously dilated, the renal structures atrophy from pressure, and the kidney becomes converted into a large cyst, *hydronephrosis*. At first the liquid is simply urine, but later, as the secretory activity of the kidney is interfered with, the mucous membrane of the pelvis and calices secretes a watery fluid. The condition is usually unilateral.

HÆMORRHAGE may occur in inflammation, from the presence of a calculus, in blood states, *e.g.* infective diseases and purpura, and from new growths.

INFLAMMATION, ureteritis, and pyelitis is usually bilateral, and is generally due to an extension from the bladder, particularly in calculus and enlarged prostate, in which case the urine is alkaline, or the stone may be in the renal pelvis, *calculous pyelitis,* which is usually unilateral. Sometimes the *B. typhosus* or *B. coli* may set up an acute pyelitis. The inflammation may be of all degrees of intensity—catarrhal, suppurative, or even gangrenous,—and sooner or later the bacteria causing the condition invade the kidney in which suppuration ensues, and the condition of surgical kidney (*purulent* *pyelonephritis*) results (see also *ante*, p. 433). Finally the whole kidney may become destroyed and converted into a bag of pus, *pyonephrosis*.

Calculous pyelitis.—Calculi are often found in the pelvis of the kidney, and vary in size from fine sand up to large branching stones moulded to the form of the pelvis and calices. The commonest varieties are uric acid and calcium oxalate. They give rise to pyelitis, pyonephrosis, and ulceration of the pelvis or ureter.

Renal colic is the intense pain associated with the passage of a calculus down the ureter.

Tuberculous pyelitis is rare in the miliary form; it is generally chronic, limited and caseous, and secondary to tubercle of the kidney or of the lower urogenital tract.

Tumours, with the exception of the *villous papilloma* like that of the bladder (p. 447), rarely occur in the renal pelvis and ureter, but carcinoma and sarcoma have been observed.

Parasites.—The bilharzia, *Filaria Bancrofti* and *Eustrongylus gigas* are met with in the renal pelvis.

Malformations of the bladder are not uncommon. It may be completely absent, the ureters opening into the urethra, vagina, or at the umbilicus. The most frequent condition is that known as extroversion, in which the anterior wall is absent, the mucous membrane being continuous with the skin of the abdomen, or the urethra may open on the upper aspect, *epispadias*, or on the under aspect, *hypospadias*, of the penis, which then is usually small and stunted. The urachus may be patulous and open at the umbilicus. Diverticula may occur, either congenital, or acquired from atrophy of the vesical wall the result of increased intra-vesical pressure from stricture, stone, or enlarged prostate.

In women the bladder may become malposed and descend into the vagina, *vaginal cystocele.*

DILATATION, HYPERTROPHY, AND ATROPHY OF THE BLADDER are secondary to obstruction to the outflow of urine (see below).

PARALYSIS of the bladder results from disease or injury of the lumbar cord and leads to distension of the bladder with overflow of urine.

RETENTION OF URINE.—*Retention* of urine is said to occur when the urinary secretion continues, but is not discharged from the bladder; *suppression* (*anuria*), when the secretory activity of the kidney is in abeyance.

Retention of urine is of two forms, obstructive and non-obstructive.

Obstructive retention is commonly caused by stricture of the urethra and prostatic hypertrophy in men, the immediate cause being congestion of the mucous membrane, and tumours of the uterus displacing the bladder and inducing kinking of the urethra in women.

Non-obstructive retention occurs in atony of the bladder, which is a frequent sequel of retention with over-distension, or may be a result of senile atrophy of the vesical walls, and in disease of the lumbar cord, causing paralysis. Hysteria is another well-known cause.

Absolute retention results in great distension of the bladder, which may reach up to the umbilicus, its walls become stretched and thinned, and if the condition be unrelieved rupture occurs, or rupture takes place through the membranous urethra. Fatal peritonitis usually ensues if the urine extravasates into the peritoneum.

In other cases the retention is only partial, and the bladder having become filled to a certain extent overcomes the obstruction, and some of its contents escape, but not all, the bladder is never completely emptied. This condition is a very frequent one in prostatic hypertrophy. A similar state often exists in non-obstructive retention from paralysis; as the urine accumulates a time comes when the pressure overcomes the resistance of the sphincter, and a passive overflow results, which is to be distinguished from incontinence.

In these cases dilatation of the bladder with hypertrophy of its walls commonly ensues, and frequently a train of events leading to the condition known as "surgical kidney" is the final sequel (see also pp. 433 and 443). Almost always micro-organisms gain access to the bladder either as a result of catheterisation or by direct extension along the urethra, the mucous membrane of which is probably in an unhealthy condition. This leads to ammoniacal decomposition of the urine and cystitis, and the residual urine lying in the base of the bladder, infection spreads up the ureters to the kidney. The increased pressure in the bladder, either owing to hypertrophy of its walls, or to its distension with urine if unrelieved, presents an obstacle to the passage of urine from the kidney into the bladder, the ureters become dilated and tortuous, the pelvis and calices dilated, the pyramids atrophied, and cortex thinned from pressure, and the kidney becomes practically a large cyst, in which, if micro-organisms gain access, suppuration ensues, and pyonephrosis or surgical kidney is the ultimate result.

Irritable bladder with constant desire to micturate is due usually to cystitis or to hyperacidity in the urine. Micturition may be unconscious (*incontinence of urine*) and due to reflex causes, *e. g.* digestive disturbance, intestinal worms, retained secretion from phimosis, and is principally seen in children.

Rupture of the bladder may be due to wounds, fracture of the pelvis, or blows on the abdomen, and is usually intra-peritoneal.

HYPERÆMIA may be active and precede or accompany inflammation, or may be passive from pressure on the vena cava, and if long continued may cause varicosity of the vesical veins, particularly at the neck of the bladder (*vesical hæmorrhoids*).

HÆMORRHAGE occurs in passive congestion and vesical hæmorrhoids, in acute inflammation, hæmorrhagic conditions, *e. g.* purpura, in trauma, and calculus, in bilharzia disease, in tuberculosis, and particularly with vesical growths.

CYSTITIS.—Inflammation of the bladder is practically always due to bacterial infection, the commonest of all being the *B. coli*, occasionally the *B. typhosus*, and frequently pyogenic cocci. A number of factors favour the growth and development of micro-organisms, viz. retention of urine from stricture, prostatic hypertrophy and lesions of the spinal cord, also the irritation of a calculus or of vesical growths, catheterisation, and exposure to cold. The inflammation may be acute or chronic, catarrhal, membranous, gangrenous, or phlegmonous. In acute cystitis the mucous membrane is injected, and may show superficial hæmorrhages and ulceration. In chronic cystitis the bladder-wall is usually hypertrophied, but sometimes atrophied, the mucous membrane pallid or yellowish, the veins prominent, and covered with mucus and urinary salts, and the urine is turbid, ammoniacal, or stinking, and deposits much mucus, pus cells, and phosphatic crystals.

Membranous cystitis may occur in advanced ammoniacal decomposition in connexion with paralysis, and may lead to extensive exfoliation of the mucous membrane.

Gangrenous cystitis occurs in acute septic conditions, trauma, and in connexion with vesical growths, and may lead to perforation.

Phlegmonous cystitis is a condition of purulent infiltration in the course of chronic cystitis, and may result in ulceration or perforation.

ULCERATION of the bladder may be due to various forms of cystitis, to calculus, frequently to tuberculosis, rarely to syphilis, sometimes to pressure of the fetal head during parturition; this may lead to vesico-vaginal fistula.

TUBERCULOSIS of the bladder is usually a part of urogenital tubercle. Tubercles develop in the mucous membrane, and soon break down into ulcers.

TUMOURS.—Simple tumours of the bladder are rare. The commonest growth is the *villous papilloma,* which consists of long, slender, polypoid masses, composed of wide thin-walled vascular loops with a small amount of connective tissue, covered with a stratified epithelium resembling that of the bladder. It may be single or multiple, does not invade the deeper layers of vesical mucous membrane, and is benign in nature, but has a considerable tendency to recur after removal. Occasionally it undergoes a carcinomatous metamorphosis. It is prone to bleed, and portions of it are easily detached.

CARCINOMA is rare as a primary growth, and is usually squamous in type, but may be villous. Secondary carcinoma, an extension from the uterus or vagina, is comparatively frequent.

PARASITES.—Bilharzia is the commonest, but the filaria and echinococcus are also met with.

CALCULI are common, particularly in certain districts, *e. g.* Norfolk and India. They are much more frequent in males than in females, partly on account of the shortness of the female urethra, so that they are more easily passed, partly because the male sex is more liable to the uric acid diathesis. Calculi are usually single, occasionally there are two or three, rarely they are multiple, and they may lie free in the bladder, or may be contained in a pouch. The usual forms are the uric acid, the uratic (composed of sodium, potassium, and ammonium urates), the phosphatic (ammonio-magnesium or calcium phosphate), and the calcium oxalate; exceptionally they may consist of calcium carbonate, cystin, xanthin, or, in combination with other material, indigo.

Uric acid calculi are small and hard, greyish-yellow or reddish-brown in colour, and on section concentrically striated. Uratic calculi are often encrusted with phosphates. Phosphatic calculi are whitish, greyish, or clay-coloured, soft and crumbling. Calcium oxalate calculi, the so-called mulberry calculi, are hard and brownish, and rough and irregular in shape. Calcium carbonate calculi are small, white, and hard; cystin are soft, brownish-yellow, and waxy; and xanthin are reddish.

Calculi are formed by deposition on some nucleus, usually an albuminous or mucous coagulum, sometimes on crystals of calcium oxalate or uric acid, on parasites or agglomerations of bacteria, or on foreign bodies. Their effect is to set up irritation and cystitis, with pain, dysuria, frequency of micturition, and hæmaturia, and, as remoter effects, hypertrophy of the bladder, pyelitis, and pyelonephritis. A stone may also become impacted in the urethra and cause retention.

The Urethra.

MALFORMATIONS.—The urethra may be absent, or defective, its roof or floor being absent or imperfect (epispadias and hypospadias). Congenital stricture may be present or the urethra be occluded by a membrane.

Wounds are not infrequent and may be caused by external violence, the passage of an instrument, calculi, and in women during parturition. If longitudinal they heal readily without bad effect, but if transverse result in stricture.

Subcutaneous rupture usually takes place in the perineal portion and is followed by extravasation of urine. In case of injury hæmorrhage occurs, the blood is bright and passed with the first portion of urine.

Urethritis.—This is almost always specific due to the gonococcus, *gonorrhœa.* The anterior portion of the urethra, particularly the fossa navicularis, is usually first attacked; the mucous membrane becomes swollen and hyperæmic, and infiltrated with leucocytes containing many gonococci, and the epithelial cells in places become detached. There is a thick yellow acrid discharge sometimes tinged with blood containing large numbers of polymorphonuclear leucocytes, a few epithelial cells, and numbers of gonococci, chiefly within the cells. As the acute symptoms pass off the discharge becomes clearer, whiter, and more mucoid, *gleet.* As the condition heals the round-celled infiltration and proliferated connective-tissue cells develop fibrous tissue, which contracts and tends to close the canal, *urethral stricture.* The gonorrhœal infection may spread to distant parts and cause epididymitis, prostatitis, periurethral abscess, and inflammation of Cowper's glands in the male, and vaginitis, metritis, salpingitis, and inflammation of the glands of Bartolini in the female, also to cystitis, pyelitis, peritonitis, arthritis, endocarditis, etc. A non-specific urethritis occasionally occurs due to trauma, gout, etc.

Stricture of the urethra is commonest in the bulbomembranous portion of the urethra, but may be met with in the spongy portion.

TUMOURS of the urethra are uncommon, squamous carcinoma may occur, but is usually an extension, fibromata (*urethral caruncle*) are met with in the female, syphilitic chancre, may be met with, but tuberculosis is rare.

The Male Genital Organs.

Malformations are occasionally met with. The penis may be stunted or absent, the prepuce redundant and constricted, *phimosis*. Absence of both testicles is rare, of one testicle less so, the other one undergoing hypertrophy, the individual being sexually unimpaired. Non-descent of the testicle (*cryptorchism*) is not uncommon; is usually unilateral and frequently accompanied with hernia; the organ may be retained in any part of the tract, generally in the inguinal canal, is usually small, but may be functionally active. True *hermaphroditism* (double sex) though developmentally possible is exceedingly rare, but false hermaphroditism is occasionally met with, ovaries or testicles being present, but the external genitals un- or mal-developed; cases have been recorded in which an ovary has been present on one side and a testicle on the other.

The Testicle.

INFLAMMATION may attack the testicle (*orchitis*) or epididymis (*epididymitis*) or both. It is usually secondary to gonorrhœa, to the passing of instruments, to external violence, and sometimes occurs in the course of infective diseases, particularly mumps. In acute orchitis the testicle is swollen and tense, and there is some effusion into the tunica vaginalis. Abscess may occur, and on resolution overgrowth of fibrous tissue may take place and interfere with the functions of the testicle. Epididymitis frequently occurs as an independent affection in gonorrhœa, the epididymis being swollen, hard, and tender.

TUBERCULOSIS of the testicle and epididymis is frequent; it may be a part of urogenital tuberculosis, but is often the primary lesion of it, and then the epididymis is generally first attacked. One or more caseous nodules may be present, usually in the globus major, or there may be many miliary tubercles. The infection is either hæmatogenous or spreads along the vas deferens from the bladder or prostate. When the disease is primary in the epididymis, the infection tends to spread to the testicle, then along the vas to the vesiculæ seminalis, and so to the bladder, and the whole urogenital tract may become involved. The tubercles are rich in giant cells, and tend to early caseation.

SYPHILIS is specially prone to attack the testicle. It occurs in two forms, either as a diffuse inflammation followed by fibrous hyperplasia or as gummata. In the first form the organ becomes hard and somewhat enlarged, and the seminiferous tubules atrophy from pressure. *Leprosy* also frequently attacks the testicle.

TUMOURS.—Many tumours of the testicle are teratomata, and present mixtures of various types of tissues, but dermoid cysts are rare. *Fibromata* occasionally occur as small nodules springing from the tunica albuginea or rete. *Adenomata* may arise from the seminiferous tubules, and are solid or cystic.

ENCHONDROMATA.—Pure cartilaginous tumours are rare but islands of cartilage are frequent in testicular growths; mucoid degeneration, calcification, or ossification may occur in them. In one remarkable case recorded by Paget an apparently pure cartilaginous tumour gave rise to *secondary cartilaginous growths in the vena cava and lungs*, and was described as a "malignant enchondroma." It was re-examined by Kanthack and Pigg[1] forty years later, and found to be in reality a carcinoma.

SARCOMA is not infrequent, is usually of the round- or spindle-celled type, and may produce tumours of enormous size. Degeneration, hæmorrhage, cystic change, and necrosis may occur. Certain peculiar large-celled sarcomata are met with, the cells resembling epithelium and enveloping plexuses of blood-vessels. These have been regarded as arising from the peculiar interstitial cells of the testicle. Sometimes there is a proliferation of the tubules (*adeno-sarcoma*), and cartilage is common.

CARCINOMA is of the adenomatous type, but is probably rare; large-celled sarcoma being mistaken for it. It seems to be not infrequently accompanied with intra-vascular secondary growths.[2] Sometimes the tumours are curious mixtures of large cells, cartilage, and muscle, and are probably teratomata.

HYDROCELE, or effusion into the tunica vaginalis, is the result of inflammation, acute or chronic. In the acute form it is associated with gonorrhœa or trauma, in the chronic it comes on insidiously and from no apparent cause. The fluid is generally clear and serous, and frequently deposits fibrinous coagula on standing. Cholesterin and blood may be present in it. The amount of fluid varies; sometimes it reaches enormous proportions. In long-standing cases the tunica becomes thickened and fibrous, and fibrous bands may divide the cavity into loculi. *Hydrocele of the cord* is a similar accumulation into the unobliterated funicular process.

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[1] *Trans. Path.* Soc. *Lond.*, xlviii, 1897, p. 150.

[2] See Kanthack and Pigg, *Trans. Path. Soc. Lond.*, xlviii, 1897, p. 139.

HÆMATOCELE is hæmorrhage into the tunica vaginalis as a result of injuries or of the hæmorrhagic diathesis.

THE SEMINAL VESICLES AND VAS are subject to inflammation in the course of gonorrhœa. *Tuberculosis* generally accompanies urogenital tuberculosis. *Cysts* containing spermatozoa and *calculi* may occur.

The Prostate.

PROSTATITIS, inflammation, may be acute or chronic. The former is common in gonorrhœa, but may be caused by instrumentation or calculi, and suppuration may ensue. The chronic form is also frequent in gonorrhœa, and leads to fibrous hyperplasia and induration.

TUBERCULOSIS is frequent as a part of urogenital tuberculosis, and is usually caseating.

PROSTATIC HYPERTROPHY.—The normal prostate weighs about 16–17 grms., and measures about 4 cm. in length and width, and 2 cm. in thickness. After the age of sixty or thereabout it frequently undergoes enlargement, something like 1 out of 3 males presenting this change. The enlarged prostate averages from 25–85 grms. in weight, but may be much more. One or all the lobes may be enlarged, often the middle lobe alone, which may project into the lumen of the urethra. The cause of the enlargement is uncertain; it has been ascribed to an arterio-sclerotic process or to chronic inflammation from undue sexual stimulation, and it has been suggested that it is analogous to a uterine fibroid, none of which theories is a satisfactory explanation. Microscopically, the change is usually an adenomatous one, dilated acini lined with a cubical epithelium lying in an abundant stroma of muscular and connective tissues (Plate XXI., A.). Some of the acini may contain peculiar concentrically-arranged bodies, giving the lardaceous reactions (corpora amylacea), which may calcify forming calculi. Prostatic hypertrophy, if of any extent, is followed by serious consequences. It obstructs the exit of urine, and leads to dilatation and hypertrophy of the bladder, the bladder is never completely emptied, cystitis ensues, the infection passes upwards to the kidney, and surgical kidney is a frequent result.

CARCINOMA AND SARCOMA are rare. The former is remarkable by the extent of the secondary metastatic growths, and their proneness to attack the bones with the development of osseous tissue.

The Penis and Scrotum.

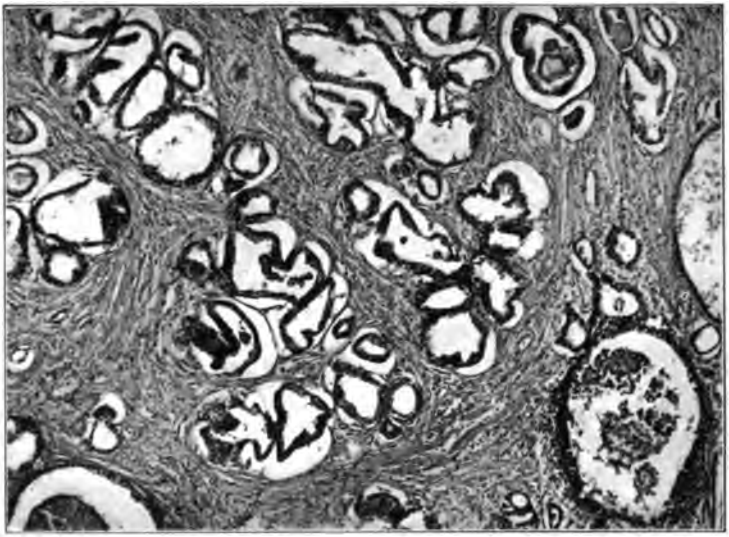
INJURIES may lead to rupture of the sheath of the corpora cavernosa and extensive, even fatal, hæmorrhage (so-called fracture).

INFLAMMATION is most frequent in the glans (*balanitis*), and may be due to irritation of retained secretions in phimosis or to gonorrhœa. Inflammation of the cavernous bodies may follow injuries, gonorrhœa, and fevers, and may lead to considerable fibrous hyperplasia.

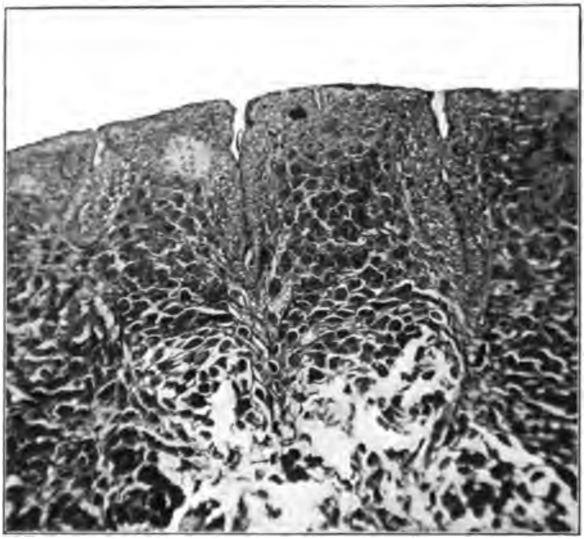
SYPHILIS.—The penis is the commonest seat of the initial chancre, particularly at the corona and frenum. Condylomata and gummata also occur. *Tuberculosis* is rare, but has been met with after a circumcision (direct infection), also by extension.

SOFT CHANCRE (chancroid) is another common venereal affection producing roundish sloughy ulcers, generally multiple, which may become phagedænic. In the

PLATE XXI.



A. Enlarged prostate (adenoma). (Hæmatoxylin and eosin, × 65.)



B. *Molluscum contagiosum* of skin, showing "molluscum bodies." (Hæmatoxylin and eosin, × 120.)

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lesions a small non-Gram-staining bacillus (Ducrey's) occurs. Suppurating inguinal buboes frequently accompany it.

TUMOURS.—Warts are common, sarcoma is rare. Carcinoma of the squamous-celled type is frequent in the prepuce and glans, where it is usually papillomatous, forming more or less cauliflower growths, and in the scrotum, particularly in chimney sweeps, tar workers, etc.

Elephantiasis has a frequent seat in the penis and scrotum (lymph scrotum). Concretions may occur under the prepuce consisting of desquamated epithelium and smegma, with urates and phosphates. The scrotum is a common seat of dropsy in renal and chronic cardiac diseases.

COWPER'S GLANDS may be involved in gonorrhœa, and the inflammation may terminate in abscess.

THE SPERMATIC CORD may become inflamed in urethritis or traumatism. Seminal cysts may develop from remains of the Wolffian body, or encysted hydrocele in the funicular process. A varicose condition of the spermatic veins is common (*varicocele*), is most frequent in young adults, and the left side is most often more extensively affected than the right, because the left vein passes behind the rectum, and enters the renal vein at a right angle (the right passes directly into the vena cava).

CHAPTER XVII.

THE FEMALE GENERATIVE ORGANS—THE MAMMA.

THE FEMALE GENITAL ORGANS.

The Vulva, etc.

Atresia or absence is rare. Adhesion of the labia sometimes occurs, congenital or following inflammation. The external genitals may remain undeveloped at puberty, in which case the uterus is absent or undeveloped. Hyperplasia of the clitoris and labia minora may be met with, and the latter is a normal condition in certain savage races, forming the apron. Inguinal hernia may pass into the labium majus. Venous congestion of the labia, with varicosity of the veins, is common in pelvic tumour, or may accompany varicose veins of the lower extremities. It also occurs in chronic cardiac disease, in which, and also in renal disease, there may be much dropsy. Hæmorrhage forming a large hæmatoma is not infrequent during parturition.

Various skin eruptions, particularly eczema, are common about the vulva; gonorrhœal inflammation is also frequent, particularly in children, and may result from infection from the mother during parturition. Pruritus is frequent, especially in diabetes. Diphtheria often attacks the vulva with the formation of membrane. Noma is met with in weak underfed children and in the course of fevers. Chancre and chancroid are frequently present about the labia, and may be followed by phagedæna; also mucous patches and condylomata. Gummata are rare, tubercles extremely so.

Kraurosis vulvæ is a rare and remarkable condition, and consists of an inflammatory hyperplasia of the connective tissue, degeneration of the connective tissue, and œdema of the epidermis and corium leading to cicatricial contraction, and stenosis of the vagina. The cause is unknown.

Warts and *fibromata* are frequently met with, and *carcinoma*, usually squamous-celled, is not uncommon, but sarcoma is rare. Elephantiasis may affect the vulva.

Bartolini's glands are commonly affected in the course of gonorrhœa. The inflammation, which is generally purulent, may last for months or even years.

The *hymen* often presents abnormalities. It may form a continuous membrane, with perforations, or be imperforate leading to retention of the menses; this may occur to such an extent as to dilate the uterus and form a large abdominal tumour. Sometimes it is so tough as to interfere with coition and parturition.

The Vagina.

Absence or atresia of the vagina is sometimes met with, and is generally associated with mal-development or absence of the uterus (but not necessarily so) and other sexual defects. Stenosis may occur, congenital, or the result of inflammation. Sometimes the vagina is divided by a septum through failure of union of the distal ends of the Müllerian ducts, and this may be associated with divided or double uterus.

Lacerations and contusions may occur from traumatism, but chiefly from parturition, and a communication be established between the bladder or rectum (vesico- or recto-vaginal fistula), or the tear may be more extensive, involving the whole perineum.

Stretching of the vagina during parturition, with separation from its muscular and fascial support, may lead to prolapse of the rectum or bladder into the vaginal cavity, *rectocele* or *cystocele*.

VAGINAL INFLAMMATION is acute or chronic, usually catarrhal, and generally the result of gonorrhœa, but may be diphtheritic, traumatic, or arise in the course of fevers. Emphysematous vaginitis may occur after parturition or other injury, ulcers from the pressure of pessaries, etc.

CHANCRES may occur, but are rarer than in the vulva. *Tubercle* is very rare.

TUMOURS.—*Cysts* are not infrequent, and arise either from embryonic remnants (Gärtner's or Müller's ducts) or from the glands, or, more frequently, from inclusions of the mucosa in repair of perineal tears.[1] Echinococcus cysts have been met with.

Sarcoma is sometimes met with in childhood or may be congenital, and is of the spindle- or round-celled variety; it is much rarer in adults.

Carcinoma of the squamous-celled type is not infrequent as a primary growth. It may also be secondary to uterine or rectal cancer.

Parasites are met with. The protozoan flagellate, the *Trichomonas vaginalis*, is common, and worms, *e. g. oxyuris*, may migrate from the intestine. The vaginal secretion being acid is inimical to bacteria.

Vaginismus, spasm of the muscles surrounding the vaginal orifice, and interfering with or preventing coitus, may be purely neurotic, or may be due to hyperæsthesia resulting from exposed nerve-terminals in the ruptured hymen, etc.

The Uterus.

Malformations of the uterus arise from faulty or arrested development of the Müllerian ducts. If the two ducts completely fail to fuse, the uterus is double—*uterus didelphys;* if the fusion be partial, the uterus may appear normal in its lower portion, but is double in its upper, the cavity being divided more or less completely into two—*uterus bicornis.* If external fusion of the Müllerian ducts be complete, but internal fusion fails, the uterus may present little or no abnormality externally, but its cavity is divided by a central septum more or less completely into two halves—*uterus duplex* or *septus.* Frequently, coincident with these abnormalities, the uterus may be rudimentary, or asymmetrical owing to better development of one half. Congenital retroversion or retroflexion has been met with. Rarely the uterus is completely absent; sometimes in the adult it retains the characteristics of childhood—*uterus infantilis.* The cervical canal is occasionally congenitally stenosed.

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[1] See *Johns Hopkins Hosp. Bull.*, June, 1905, p. 207.

Acquired malpositions of the uterus are frequent. The whole uterus may be rotated backwards on its transverse axis—*retroversion*, or forwards—*anteversion;* or the uterine body may be bent where it joins the cervix—*retro-* or *ante-flexion.* It may also be displaced bodily, or twisted, or may descend—*prolapse.* Various factors conduce to these malpositions: incomplete involution after parturition, or the presence of tumours increasing its size and weight, softening from inflammation, relaxation of the abdominal parietes and uterine ligaments, and destruction of the perineal floor.

Inversion of the uterus, partial or complete, is met with during labour, from traction on the cord, etc.; occasionally from a uterine polypus.

Stenosis of the uterine cavity or cervical canal may result from inflammation, obstruction by tumours, etc.

Hæmatometra—distension of the uterine cavity with menstrual blood—occurs from cervical stenosis or atresia of the vagina, or imperforate hymen. Fluid or pus may also collect in the uterus, sometimes gas.

Rupture of the uterus may occur during labour, and lacerations of the cervix are frequent, and often accompanied with a rolling back of the edges—*ectropion.*

Hypertrophy of the cervix results from inflammation.

Dysmenorrhœa, painful menstruation, may be due to a stenosed cervical canal, to exfoliation of large masses of the mucosa (membranous dysmenorrhœa), but frequently no cause can be assigned.

Endometritis, corporeal or cervical, according as it affects the uterine body or cervix, is the name applied to inflammatory changes in the uterine mucous membrane. It presents several varieties, and may be simple or infective.

In *glandular endometritis* the glands are enlarged or increased in number, or both, the mucous membrane is thickened and softened, but the inter-glandular stroma is but little affected. In *interstitial endometritis* there is a diffuse hyperplasia of the inter-glandular stroma with atrophy of the glands. *Membranous dysmenorrhœa* histologically is an interstitial endometritis in which the endometrium is shed *en masse* or in pieces.

Gonorrhœal endometritis is common, and is mainly interstitial. Other micro-organisms may set up an acute septic endometritis, which may lead to abscess formation in the uterine walls.

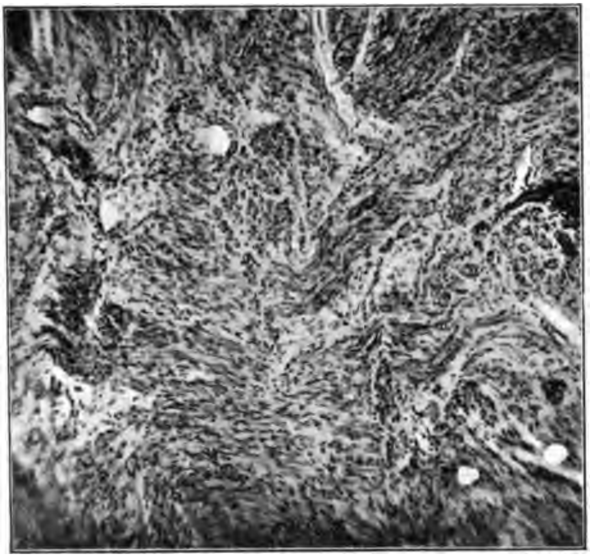
Cervical erosions are inflammatory, and appear as sharply-defined, intensely red, sometimes velvety patches. The squamous is converted into cubical epithelium, and glandular cysts (Nabothian) may be present, giving rise to a nodular condition.

Metritis, inflammation of the uterine muscle, is acute or chronic. The acute form is generally infective, usually gonorrhœal. The uterine wall is thickened and softened, and infiltrated with round cells, and occasionally abscesses form. Chronic metritis may follow the acute form, but is commoner as a result of subinvolution. There is considerable connective-tissue hyperplasia.

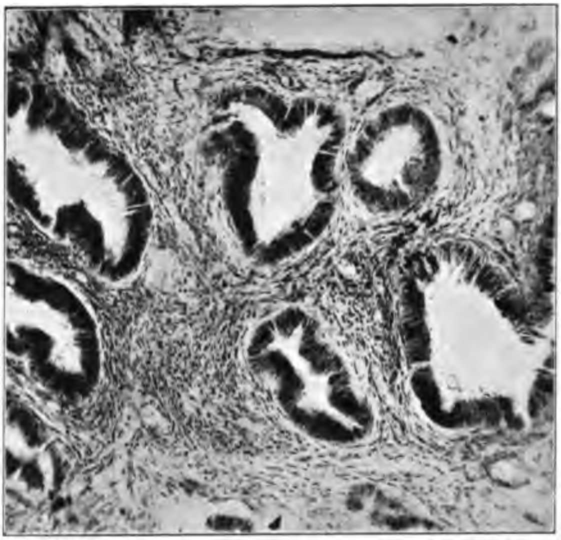
Tubercle and *syphilis* of the uterus are uncommon. The former is usually secondary to that of the tubes.

Tumours.—The commonest of all uterine tumours is the so-called *fibroid*. This is usually a fibro-myoma composed of connective tissue and unstriped muscle (Plate XXII., a.). It may be single or multiple, varying in size from a pea to a cocoanut, but may reach enormous dimensions, and is situated either under the peritoneum (sub-serous), in the myometrium (interstitial), or is sub-mucous, and may form a polypoid mass. The tumours contain varying proportions of connective and muscular tissues together with large arteries and venous sinuses. Various changes may occur in the growths, fatty or myxomatous degeneration, calcification, and inflammation, necrosis or gangrene. Their causation is unknown. Occasionally they are combined with adenomatous, adenomyomatous, or sarcomatous changes.

Mucous polypi, consisting of a localised hyperplasia



A. Fibro-myoma of the uterus. (Hæmatoxylin and orange-rubin, × 50.)



B. Adenomatous polypus of the uterus. (Hæmatoxylin and eosin, × 75.)

of the mucosa, are not infrequent. Adenomata also occur (Plate XXII., B.).

CARCINOMA.—In the vaginal cervix, the squamous-celled variety is the commonest and frequently forms pedunculated and cauliflower masses. Columnar-celled carcinoma also occurs, arising from the glands; this form may also develop from the cervical endometrium. In the body of the uterus columnar-celled carcinoma occurs and is of an adenomatous type, forming nodules, polypi, or villous outgrowths on the endometrium. What is apparently a simple adenoma frequently develops into an adeno-carcinoma.

SARCOMA generally arises in the uterine body and is usually a myosarcoma.

Various foreign bodies and echinococcus cysts may be met with in the uterus.

PERIMETRITIS, inflammation of the peri-uterine connective tissue and peritoneum (pelvic peritonitis), frequently follows puerperal inflammation of the uterus, tubes, etc.

PARAMETRITIS, inflammation of the pelvic connective tissue of the broad ligament, iliac fossæ, etc., usually results from puerperal sepsis.

Pathology of the Pregnant Uterus.

Decidual endometritis may ensue on a pre-existing endometritis. Puerperal endometritis or metritis may occur, and is usually septic.

PUERPERAL SEPSIS, puerperal fever, may be a toxæmia (sapræmia) from absorption of decomposing matter in the uterus, or a septicæmia or pyæmia, resulting from infection of lacerations of the cervix, vagina, or perinæum, or of the placental site. The micro-organisms causing it may be various, streptococci only in something like a quarter of the cases, but frequently associated with other forms, *e. g. B. coli* and staphylococci, the *B. coli* alone, *M. pneumoniæ,* etc.[1] The part which may be played by gonococci is uncertain. In puerperal pyæmia there is generally a streptococcic infection of the venous thrombi at the placental site.

PLACENTAL POLYPUS.—Retention of a portion of the placenta may result in the formation of a polypoid mass.

INVOLUTION of the decidua may be incomplete, decidual cells remaining long after labour or miscarriage, and a condition of endometritis, interstitial or glandular, ensues.

HYDATIDIFORM MOLE, the conversion of the placenta into a cystic mass, seems to be a mucoid degeneration.

CHORION EPITHELIOMA, syncytioma malignum, or deciduoma malignum, is a form of malignant disease of the uterus occurring after pregnancy which has recently attracted much attention. In something like half the recorded cases it has followed the discharge of a hydatidiform mole. The growth forms a soft, spongy, nodular, or cauliflower mass attached to the endometrium, light or dark red in colour, very vascular, and frequently containing hæmorrhages. It tends to infiltrate the uterine wall, and metastases occur in the neighbouring parts, in the lungs, and more rarely in other organs, being carried by the blood-stream up to a late stage, when lymphatic infection may take place. Leith[2] thus describes the histological characters in a typical case: "The tumour is mostly composed of blood-clot, with comparatively small processes composed of epithelial cells towards its outer part, where it borders upon the inner wall of the uterus (Plate XXIII., A.). Some of these have a more or less distinct tubular formation. The interior of many of the tubes shows an irregular space, which in a few is occupied by a fibrous tissue with blood-vessels. The most favourable of these tubes are easily recognised as villi with a hypertrophied epithelial covering. The epithelial cells are arranged in the two layers typical of a villus, the outer syncytial and the inner polyhedral or Langhan's layer. The proportionate amount of these varies greatly in the different processes, the syncytial cells being usually fewest in the most typical villi. The fibrous tissue core of the villus tends to degenerate and disappear, and the empty, irregular, tubular spaces may be villi in which this change has taken place. It is possible also for the epithelial cells to aid in the absorption and disappearance of their own fibrous cores in the same way as they cause the absorption of the tissues of the uterine wall. On the other hand, the evidence of the absorption of the uterine wall by the epithelial cells is very obvious. These cells are, however, mostly separated from the muscle-fibres of the uterus by a protective fibrous tissue layer of new formation, and, when the invading cells form an obvious villus-like process, representatives of both layers are seen in varying proportions, but where the invasion of the uterine wall is earliest, as in the thin thread-like processes of cells, or in isolated individual cells, they are all apparently of a syncytial type. The walls of the uterine blood-vessels are directly invaded in the same way as other uterine tissues; hence the epithelial cells gain entrance into the circulation, and may be seen in greater or less numbers in many of the vessels with intact walls which lie at some distance from the tumour. Many of these cells may die, but others may survive and form the nuclei of new growths elsewhere in the uterine wall or in distant organs."

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[1] See Foulerton, *Practitioner,* March, 1905, p. 387.

[2] *Brit. Med. Journ.,* 1904, ii, p. 1392.

The Fallopian Tubes.

Absence of both tubes accompanies failure of development of the other genital organs. One tube is absent in uterus unicornis. Various accessory tubes, ostii, and fimbriæ may be present. Displacements of the tube or torsion may accompany similar conditions of the uterus, ovarian and uterine tumours, and inflammation. *Hæmatosalpinx,* distension of the tube with blood, may occur in hæmatometra and tubal pregnancy.

SALPINGITIS, inflammation, is usually secondary to gonorrhœa or puerperal sepsis by direct extension. It may be limited to the mucous membrane, *catarrhal,* but usually involves the whole thickness of the wall of the tube. Through adhesions both openings of the tube may be closed, and if suppuration occurs, as is not uncommon, *pyosalpinx* is the result. In some cases of mild inflammation, with closure or stenosis of both openings, the tube may become dilated with a serous fluid, *hydrosalpinx.*

TUBERCLE of the female genital tract has its most frequent seat in the tubes. It is usually secondary, but often primary. It is generally an acute diffuse form, with rapid and extensive caseation. Syphilis, malignant growths, and parasites are rare. Cystic tumours formed by occlusion and dilatation of the end of the Müllerian duct may occur, the *hydatid of Morgagni.*

EXTRA-UTERINE GESTATION is the development of the fertilised ovum in the ovary or any part of the tube, rarely *from the first* in the abdominal cavity into which the ovum has dropped. The cause is obscure. It is most commonly tubal.

The Ovary.

The ovaries may be absent, infantile, or rudimentary, and accessory ovaries have been described. The ovary may be displaced with the uterus, and may be found in the sac of a hernia, generally inguinal or femoral. Hyperæmia and hæmorrhage occur in general venous stasis, new growths of the uterus, injury, and fevers.

Ovulation is accompanied by certain phenomena. When a ripe Graafian follicle ruptures, the cavity becomes filled with blood, which undergoes the ordinary changes of extravasated blood, with fatty change at the edge and development of a yellow colour, the whole forming the corpus luteum. Ultimately a small cicatrix is formed. When fertilisation occurs the corpus luteum is usually much larger than when unfertilised.

Hypertrophy has been described, and atrophy is physiological at the climacteric, but may result from hæmorrhage, inflammation, etc.

OÖPHORITIS, inflammation, may be acute or chronic. *Acute oöphoritis* occurs in septic infection and puerperal sepsis, fevers, and gonorrhœa. In septic infections the streptococcus or the *B. coli* is usually the causative organism. The inflammation is generally diffuse, the ovary is swollen and hyperæmic, hæmorrhages may be present, the tissues are infiltrated with leucocytes, and the germinal and follicular epithelium degenerate. Abscess may form or the whole ovary necrose. As a metastatic condition oöphoritis may be met with in measles, scarlatina, typhoid fever, and particularly in mumps. Frequently the inflammation spreads to the surrounding cellular and peritoneal tissues.

Chronic oöphoritis results from long-standing and recurrent hyperæmia caused by chronic heart and hepatic diseases, alcoholism, sub-involution, and tumours of the uterus, etc. There is interstitial fibrous hyperplasia with degeneration of the epithelium, the vessel walls become thickened, and an arteritis obliterans may be present, and the ovary may finally become nodular, contracted, and sclerotic, "cirrhosis of the ovary."

TUBERCULOSIS is not infrequent as a secondary infection from the tubes or peritoneum. It may be miliary, or chronic and diffuse with caseation and abscess. Parasites are rare.

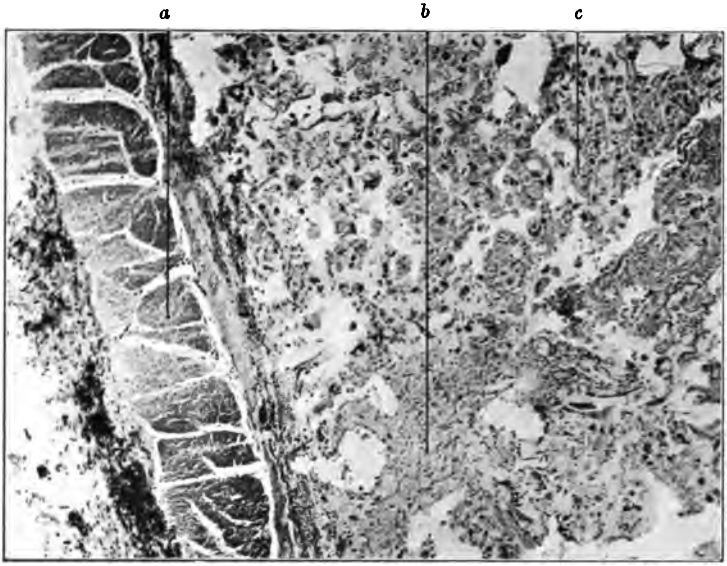
RETENTION CYSTS of the ripe or of the ruptured Graafian follicles or corpus luteum may occur. They may be either single or multiple; in the latter case the ovary may be as large as an orange, and consists of a mass of cysts, which contain a simple serous fluid.

PROLIFERATING NEW GROWTHS of the ovary may be divided into two classes, those derived from the parenchyma, and those derived from the stroma. The parenchymatous growths are epithelial, and include various forms of cystoma, adenoma, and carcinoma; the stromatogenous growths are fibromata and sarcomata. In addition there are the dermoids and teratomata derived from the ovule.

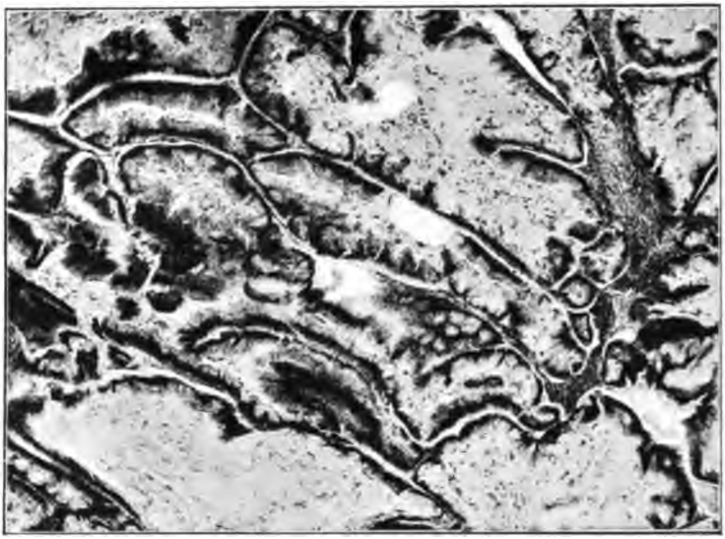
CYSTOMATA are of various kinds. The *simple serous cystoma* is not common, is usually multilocular and benign, and may reach large dimensions; its walls are lined with a cubical epithelium, and there are rarely any papillary ingrowths. The cyst is filled with a serous fluid containing a little fat, epithelial cells, and cholesterin crystals.

Cystadenoma is the most frequent form of ovarian cyst. It is a multilocular cystoma, generally unilateral, benign and pedunculated, lined with a single layer of

PLATE XXIII.



A. Chorion epithelioma. *a*. Wall of the uterus. *b*. Blood-clot. *c*. Mass of villi covered with epithelial cells. (Picrocarmine, × 35.)



B. Cystic adenoma of the ovary. (Hæmatoxylin and eosin, × 55.)

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cubical epithelium, and filled with a mucoid-like fluid, pseudomucin (Plate XXIII., B.). It may reach enormous dimensions, and has a plentiful blood supply by vessels contained in the pedicle. Various changes may occur in the tumour, the epithelium may become degenerate or necrotic, hæmorrhage may occur into it, and the walls become calcified. The fluid contents sometimes contain gelatinoid masses of colloid substance. The pseudomucin (formerly called metalbumin) differs from mucin in not being precipitated by acetic acid.

The ætiology of the tumour is unknown. Although usually regarded as benign it is to be noted that intraperitoneal rupture may lead to metastatic cystadenomata of the peritoneum, and apparently such growths may become carcinomatous. In some cystadenomata papillary growths may be present, and these tumours, if they rupture, are very liable to give rise to extensive papillary growths in the abdomen.

Parovarian cystoma is a cystic dilatation of the tubules of the parovarium. The wall is lined with a ciliated cubical epithelium which in large growths of long duration may become converted into a non-ciliated flattened epithelium. The contained fluid is serous and alkaline, sometimes turbid from admixture with altered blood.

Ovarian tumours produce various pressure effects according to their size, and may undergo inflammation and suppuration, rupture, or torsion of the pedicle sufficient to cause necrosis and gangrene. Hæmorrhage may also occur into their interior.

Certain peculiar growths met with in the broad ligaments and in connexion with the ovaries and uterus seem to be derived from adrenal rests.

CARCINOMA of the ovary is infrequent, and is usually of a cystic adenomatous structure.

DERMOID CYSTS constitute some 5 per cent. of all ovarian tumours; they are thin-walled cysts which may contain a variety of structures, sebaceous and sweat-glands, hair follicles and hair, epithelium, teeth, connective tissue, muscle, bone and rudimentary limbs, and may occur in the young as well as in adults. *Teratomata* are very rare, contain structures similar to those of the dermoid, and in addition proliferating embryonal connective tissue (*i.e.* of a sarcomatous type), and are excessively malignant.

FIBROMA AND FIBROMYOMA occur in the ovary, and may be large, but are not common.

SARCOMA is usually of the spindle- or round-celled type, and is more frequent in children than in adults, and frequently undergoes myxomatous change. Endothelioma is also met with.

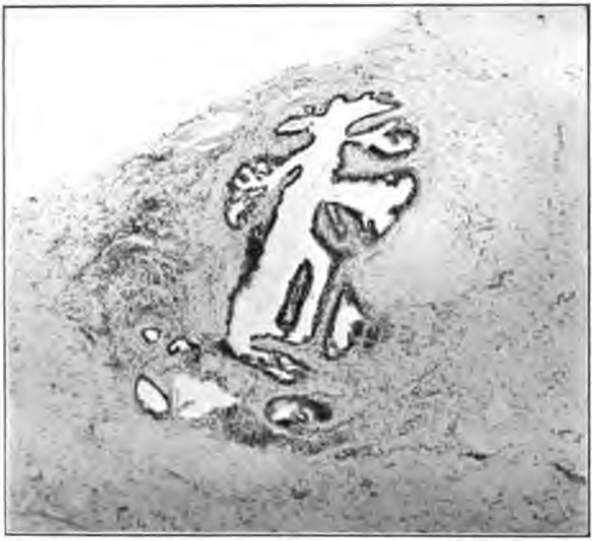
The Mammary Gland.

The mammary gland develops as an ingrowth of the epidermis and originates from sudoriparous glands. At puberty in the female the epithelial elements proliferate and form acini. These increase in number during pregnancy and lactation, but at the menopause undergo atrophy with increase in the fibrous and adipose tissues.

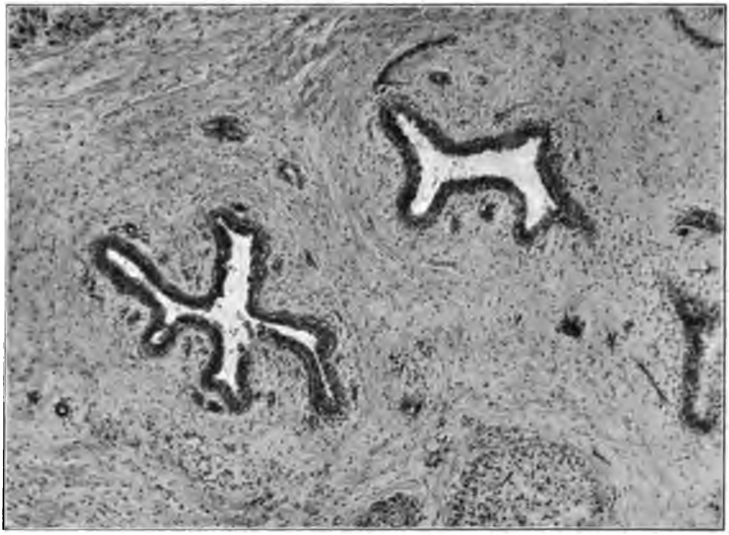
Abnormalities of the breast are not infrequent; it may be absent or remain infantile, and supernumerary breasts, generally about the axilla, are not uncommon. Hypertrophy of the breast, which may assume an enormous size, is a rare condition, and seems to be due to adenomatous or fibromatous change.

MASTITIS, inflammation, may be acute or chronic. The acute form is generally seen at the commencement of lactation, and is usually due to infection through

PLATE XXIV.



A. Chronic mastitis. (Hæmatoxylin and orange-rubin, × 40.)



B. Fibro-adenoma of the breast. (Hæmatoxylin and orange-rubin.
× 55.)

To face page 468.

the nipple with staphylococci or streptococci. The breast becomes tender, swollen, and infiltrated, and suppuration is common.

Chronic diffuse mastitis may be the result of acute inflammation, or may be chronic (*e. g.* syphilitic) from the first. There is hyperplasia of the connective tissue with atrophy of the gland acini, sometimes cystic formation (Plate XXIV., A.), and more or less of the gland may be converted into a hard fibrous mass, which may be mistaken for scirrhus.

Tuberculosis is rare, and usually consists of one or more caseating foci.

Syphilis.—The breast or nipple may be the seat of a primary chancre, mucous patches, eruptions, gummata, and of a diffuse syphilitic mastitis.

Tumours.—Fibroma and adenoma are common, and various combinations of the two occur, fibro-adenoma. The fibroma is circumscribed and encapsuled, and consists of a dense fibrous tissue with little or no gland structure, and cysts are often present in it (Plate XXIV., B.). Pure adenomata are infrequent.

Retention cysts may occur during the active period of the gland. If they contain milk they are known as galactoceles.

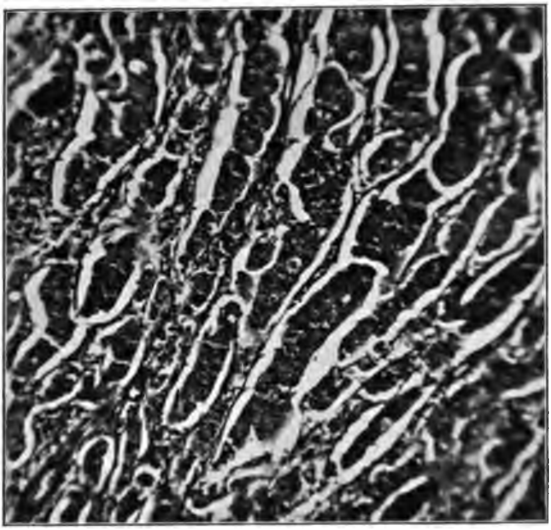
Carcinoma.—The breast is one of the most frequent seats of carcinoma. The commonest form is the *scirrhous carcinoma.* In scirrhus the bulk of the tumour consists of a dense fibrous tissue, scattered through which are groups and columns of epithelial cells; these are more numerous towards the periphery (Plate VII.). The contraction of the fibrous tissue causes the shrivelled appearance of the breast and retraction of the nipple so often present. The rate of growth varies much; frequently in old and thin people the disease hardly progresses, and after a time may practically cease, and occasionally retrogress (atrophying scirrhus). If the skin becomes involved, the tissues break down and ulceration occurs. Sometimes the growth may spread laterally and superficially, so that the thorax becomes more or less enclosed in the carcinomatous mass (cancer *en cuirasse*).

Medullary carcinoma also occurs; in this the cells are far more numerous than in the scirrhus, occasionally so numerous that there is little intervening fibrous stroma. The cells form large masses and columns closely packed together, and they frequently undergo fatty degeneration and necrosis.

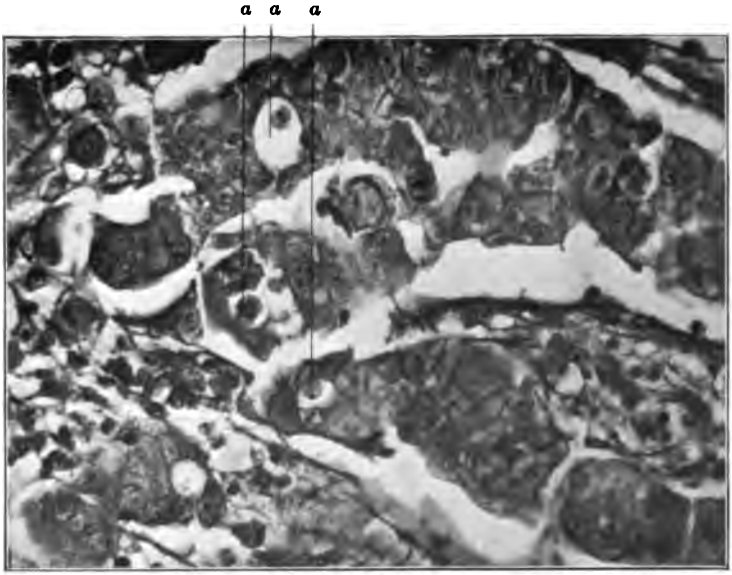
Colloid is another rare form of breast cancer.

Paget's disease of the nipple, Darier's disease, or malignant papillary dermatitis, usually affects the nipple and adjacent skin, but is occasionally met with on the penis, scrotum, and other parts. It appears as a scabby, eczematous, or deep red raw patch, which will not heal, and almost always terminates in cancer. Microscopically, there is an increase in the epithelium, and columns of ingrown epithelial cells appear in a matrix of inflammatory cells (Plate XXV., A.). Here and there an epithelial cell appears vacuolated, the vacuole containing a nucleus (Plate XXV., B., *a, a, a*). These structures have been supposed by Wickham, Darier, and others to be protozoan organisms, allied to the coccidia, termed psorosperms, and hence the disease has been regarded as parasitic in nature, and since it terminates in cancer, has lent weight to the parasitic theory of cancer formation; probably, however, they are due merely to vacuolation. Cell-nests are not found in the cancer that develops, which has been regarded as originating from the lining epithelium of the galactiferous ducts.

PLATE XXV.



A. Paget's disease of the nipple, showing the columns of epithelial cells. (Hæmatoxylin and eosin, × 50.)



B. Paget's disease of the nipple. The same as A, but more highly magnified, and showing the supposed parasitic bodies, *a*, *a*, *a*. (× 250.)

Another condition which has been ascribed to psorosperms is molluscum contagiosum, which occurs as nodules in the skin and seems to be infective. The nodule contains cavities within each of which several curious ovoid bodies occur, the supposed psorosperms (see Plate XXI., B.). They are probably really altered epithelial cells.

Metastasis in breast cancer takes place in the axillary and cervical glands, in the skin, fascia, muscles, and bones of the surrounding region, and later in the mediastinum and viscera.

SARCOMA of the breast is uncommon, and may be small or large round-, spindle-, or giant-celled. At about puberty a form of cystic sarcoma is sometimes observed. The tumours may undergo various degenerative changes.

THE MALE BREAST is not often involved. At puberty it may undergo some enlargement with pain. Rarely it may become as developed as in the female (*gynæcomastia*). Scirrhous cancer may occur.

CHAPTER XVIII.

ARRANGEMENT AND FUNCTIONS OF THE NERVOUS SYSTEM—SOME GENERAL DISORDERS AND DISEASES OF THE NERVOUS SYSTEM—MALFORMATIONS OF THE CENTRAL NERVOUS SYSTEM—DISORDERS OF THE CIRCULATION AND VESSELS—AFFECTIONS OF THE MEMBRANES—DISEASES OF THE BRAIN—THE CHOROID PLEXUS—DISEASES OF THE SPINAL CORD—PRIMARY DEGENERATIONS OF THE CORD—MUSCULAR ATROPHY—THE PERIPHERAL NERVES.

The Structure and Arrangement of the Nervous System, etc.

The central nervous system is composed of the *nerve-cells* of the grey matter of the brain, spinal cord, and spinal ganglia, with their processes, of *nerve-fibres*, which are prolongations of the processes of the nerve-cells, and of a delicate sustentacular connective tissue, the *neuroglia*, which, however, like the rest of the nervous system, is of epiblastic origin. Nerve-cells may be uni-, bi-, or multipolar, according to the number of processes which they give off, but only one special process, the *axis-cylinder process*, becomes continued into the nerve-fibres, which, in the central nervous system, are mostly devoid of a primitive sheath. A typical multipolar nerve-cell is called a neurone; it has only one axis-cylinder process, or axon, which gives off branches from each side, collaterals, which ramify in the neighbouring substance, and a number of branching processes, dendrons, which spread like the branches of a tree, and are contiguous to, but never join with, dendrons from neighbouring cells.

The nerve-cells and their branches, therefore, are anatomically distinct from one another, but they are in close physiological association, and form two series of projection systems, the efferent or motor and the afferent or sensory.

The efferent neurone consists of an upper motor neurone, starting in the cortex, and of a lower motor neurone, starting in the nerve-cells of the anterior horns of the cord. The upper neurone commences in the pyramidal cells of the cortex in the Rolandic area, and, by association fibres, is connected with other convolutions, and the axons pass through the internal capsule, giving off collateral branches, which communicate with the corpus striatum and corpus callosum and also with the cortex of the opposite hemisphere, through the medulla, where the greater number decussate and pass down the cord in the crossed pyramidal tract of the lateral columns, a smaller number passing down the direct pyramidal tract on the same side of the cord. The axis cylinders then break up into arborisations round the cells of the anterior horns. The lower neurone commences in the multipolar cells of the anterior horns, the axis cylinders of which pass to the muscles as the motor nerves.

The afferent or sensory neurones commence in the spinal ganglia, the axis cylinders of which bifurcate, one bifurcation passing to the skin as a sensory nerve fibre, the other entering the cord, passing upwards and becoming associated by collateral branches and arborisations with the motor cells of the anterior horns, and with the cells of the posterior horn and of Clarke's column. Branches of the axis cylinders pass upwards in the direct cerebellar tract, becoming physiologically connected with the cerebellum, and in the posterior columns to the nucleus gracilis and nucleus cuneatus in the medulla, to the optic thalamus, and to the cortical grey matter.

The nerve-cell.—A nerve-cell when stained with thionin or methylene blue, appears as an irregular mass with processes and a nucleus. The body of a cell consists of a cytoplasm, which as a whole hardly stains, but contains irregular granules which stain deeply, the Nissl granules. The nucleus does not stain, but remains as a clear space near the centre of the cell, and contains a round, deeply staining nucleolus (Fig. 12, *a*). The cytoplasm is fibrillated, the fibrillæ passing into the processes. The integrity of a nerve-cell depends to some extent on its functional activity, and amputation or disuse of a limb results in atrophy of the nerve-cells from which the nerve supply of the limb is derived. Injury to the axis cylinder process likewise induces degeneration and atrophy. The nerve-cell itself may also be directly affected by poisons—*e. g.* strychnine, bacterial toxins, ricin, etc. The degenerative changes occurring in a nerve-cell, in order, are swelling of the protoplasm, disappearance of the Nissl granules (*chromatolysis*), so that the cytoplasm appears filled with fine dust, swelling of the nucleus, which also becomes granular (Fig. 12, *b*), varicosity of the processes, which may become fragmented, and lastly shrinkage of the cell and vacuolation of the cytoplasm.

Degeneration of nerve-fibres.—If a mixed nerve be divided, degeneration rapidly follows *below* the lesion down to the ultimate nerve-endings, more slowly *above* the lesion as far as the next node. The rapid and marked degeneration of the distal segment of the nerve-fibre is known as *Wallerian degeneration*; the slower atrophic change in the proximal segment is known as *disuse atrophy*. The Wallerian degeneration is most prominently seen in the medullary sheath, which undergoes fragmentation into irregular droplets of myelin; the axis cylinder also fragments, and on this depends the loss of function, and the nuclei of the primitive sheath or nurilemma (if present) undergo multiplication. In the central nervous system, in which the nerve-fibres have no sheath, an overgrowth of neuroglia occurs. The changes in the medullary sheath form the basis of the various histological methods employed to detect degeneration. It seems that in the degenerated medullary sheath the lecithin or phosphorised fat is split up with the formation of phosphoric acid, choline (see p. 477), and olein, and the free olein now stains black with osmic acid (as in the Marchi method—osmic acid and Müller's fluid).[1] In the cord Halliburton

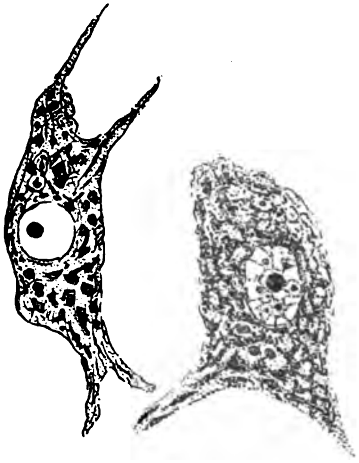


FIG. 12.—A nerve-cell stained with methylene blue—*a*, a normal cell showing the Nissl granules, processes, and nucleus; *b*, a degenerate nerve-cell showing swelling of the cell, disappearance of the Nissl granules, swelling, and granulation of the nucleus, etc.

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[1] See Halliburton, *Biochemistry of Muscle and Nerve*, 1904, p. 142.

and Barratt have shown that the ethereal extract from the degenerated side is more abundant, and contains less phosphorus than on the healthy side.

If the divided nerve be sutured, regeneration may ensue. Almost certainly the axis cylinder is regenerated by a distal outgrowth from the process of the nerve-cell from which it originates, the medullary sheath being derived from the axis cylinder. The neurilemma cells also become elongated and arranged in strands, and appearances of this kind have probably originated the idea that nerve-fibres may have a peripheral origin. The neurilemma cells may be related, probably nutritionally, to the successful repair of a divided nerve, and where they are absent—*e. g.* in the central nervous system—regeneration does not occur.

Section of an anterior spinal root leads to Wallerian degeneration below the injury, but is restricted to the *efferent* fibres of the mixed nerve.

Section of a *posterior* spinal root separates the axis cylinders from the nerve-cells in the spinal ganglion from which they originate, and Wallerian degeneration progresses upwards in the root attached to the cord, and in the tracts in the cord through which the afferent fibres pass. These tracts are mainly the postero-internal, or Goll's column, and the postero-external, or Burdach's column.

Section of the spinal cord leads to degeneration, both above and below the lesion (Plate XXVI., A.). The tracts of ascending degeneration are Goll's column (Fig. 13, *a*), Burdach's column (*b*), direct ascending cerebellar (*c*), the antero-lateral, or crossed cerebellar (Gower's) tract (*f*), and Lissauer's tract (*i*). The tracts of descending degeneration are the crossed pyramidal tract (*d*), the comma tract (*e*), the antero-lateral descending (*g*), and the direct pyramidal tract (*h*). The comma tract represents *afferent* fibres, which are *descending* in the cord, and hence the degeneration of this tract is a descending one.

Cerebral localisation.—The cortical motor centres are mainly situated in the ascending frontal convolution, in front of the fissure of Rolando, the areas of representation from above downwards being leg, arm, and face. The motor speech centre is localised in the posterior part of the left inferior frontal convolution, visual impressions are localised in the occipital lobes, auditory ones in the temporo-sphenoidal lobes, and on the left side the memory of spoken words is registered.

The cerebro-spinal fluid.[1]—The normal cerebro-spinal fluid is a clear watery fluid, which has a specific gravity of 1006. It has a slightly alkaline reaction, contains traces of proteid only, contains a reducing body (formerly stated to be pyrocatechin, but now proved to be dextrose), and is continually being secreted, probably mainly by the choroidal plexus of the lateral ventricles. Cases have been recorded of a continual dripping of the fluid from the nose. The cerebro-spinal fluid fills up all spaces, cracks, and crevices in the subarachnoid space and its annexes, a quantity proportional to the amount secreted continually escaping. The pressure on the whole cerebro-spinal axis is thus uniformly maintained, but where the vessels of the pia-arachnoid run in the sulci or dip into the substance of the brain, the layer of the arachnoid follows like a sleeve, forming thus a canalicular system in the nervous substance and containing cerebro-spinal fluid. This canalicular system is called the perivascular lymphatic system; it does not contain ordinary lymph, but the cerebro-spinal fluid, which apparently plays the part of lymph in the central nervous system.

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[1] See Mott, *British Medical Journal*, 1904, vol. ii, p. 1554.

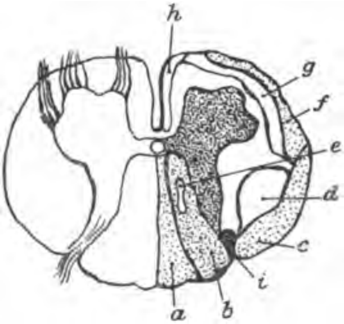

FIG. 13.—Diagram of tracts in the spinal cord (after Sherrington): *a*, postero-internal, or Goll's column; *b*, postero-external, or Burdach's column; *c*, direct ascending cerebellar tract; *d*, crossed pyramidal tract; *e*, comma tract; *f*, antero-lateral, crossed cerebellar, or Gowers' tract; *g*, antero-lateral descending tract; *h*, direct pyramidal tract; *i*, Lissauer's tract.

The brain does not appreciably waste in cases of starvation, and it has therefore been supposed that the metabolism of the brain is very small but extremely complex, and that the products of activity are continually being neutralised and removed by the cerebro-spinal fluid. The alkalinity of the fluid is only about half that of the blood, and it has been supposed that the products of nervous activity are acid, thus reducing the alkalinity of the fluid.

The composition of the cerebro-spinal fluid often becomes altered in disease: in uræmia urea is present, in diabetes the sugar is increased, and in pneumonia the chlorides are more abundant; in jaundice, however, bile-staining does not usually occur.

Halliburton and Mott have shown that choline is present in the fluid and in the blood in cases in which active nerve-degeneration is in progress, and the detection of this substance has therefore been proposed as a test to distinguish an organic from a functional affection. Ten c.c.'s of blood are usually sufficient to give the test in marked cases. The blood may be precipitated with alcohol, the mixture evaporated to dryness at a low temperature, extracted with absolute alcohol, the alcoholic extract evaporated to dryness, and the residue again extracted with *water-free* absolute alcohol. Choline gives octahedral crystals with platinic chloride, and physiologically it produces a temporary fall in arterial pressure, which is prevented by previous atropinisation of the animal.[1] Further reactions are detailed by Rosenheim.[2]

The normal cerebro-spinal fluid contains practically no organised elements, and a leucocytosis of the fluid is one of the earliest signs of organic disease of the central nervous system. Acute diseases are associated with a polymorphonuclear, chronic diseases with a lymphocytic, leucocytosis. The *Diplococcus intracellularis* appears in epidemic cerebro-spinal meningitis, the pneumococcus, gonococcus, and pyogenic cocci in other forms of meningitis; the tubercle bacillus may be detected by the inoculation test (not microscopically) in tuberculous meningitis, and the trypanosoma is found in the centrifuged fluid in sleeping sickness.

Sleep and narcosis.—Various theories have been propounded to account for sleep—*e. g.* that it is due to anæmia of the brain, to carbonic acid intoxication, to an auto-intoxication by waste products, etc. Histological theories are equally unsatisfactory. *Narcosis* may be due to a chemical interaction between the nerve-proteids and the narcotising agent. Moore and Roaf have found that chloroform forms an unstable compound with proteid.[3]

Certain Phenomena caused by Diseases of the Nervous System.

Coma, or insensibility, the ablation of the higher psychical activities, occurs from many conditions—*e. g.* syncope, apnœa, narcotic poisoning, auto-intoxication, as in uræmia and diabetic coma, epilepsy, and in gross disease, embolism, thrombosis, and hæmorrhage, tumour, meningitis, etc. Anæmia and lack of oxygen is a common feature in many, if not in all, of these conditions.

Delirium may be regarded as an abnormal stimulation of the parts of the nervous system which have to do with the higher psychical activities.

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[1] See Halliburton, *Biochemistry of Muscle and Nerve,* pp. 117-131.

[2] *Journ. of Physiology,* vol. xxxiii, No. 3, 1905, p. 220.

[3] *Proc. Roy. Soc. Lond.,* 1904, lxxiii, p. 382.

Spasm and convulsions.—Spasm may be *tonic,* slow and prolonged contraction of the muscles, or *clonic,* rapid contraction and relaxation of the muscles. The term "spasm" is usually applied when a muscle or group of muscles is involved, "convulsion" when the whole muscular system of the body is more or less involved. Tonic spasms are markedly seen in degeneration of the pyramidal tracts in which the influence of the cells of the upper efferent neurone on those of the lower motor neurone is inhibited. Local tonic or clonic spasms may also result from irritation of a cortical motor centre, or of a peripheral nerve—*e. g.* by tumours, inflammation, etc.

Convulsions may be caused by toxic agents—*e. g.* the uræmic poison, strychnine, tetanus toxin, etc., and may be due either to a direct action on the nerve-cells or to alterations in the cerebral circulation. In asphyxia the deficiency of oxygen and excess of carbonic acid act as stimulants to the nerve-cells.

In *epilepsy* no structural alterations can be detected. The convulsions are assumed to be due to a sudden discharge of nerve energy by the cortical motor cells. At the moment of the attack a sudden anæmia of the brain occurs, the result probably of vasomotor spasm. Brown-Séquard has shown that guinea-pigs may be rendered epileptic in various ways—*e. g.* by hemisection of the cord, injury to a nerve, such as the sciatic, etc. The fits, at first possessing the character of mere reflex spasm, increase in severity, until a true epileptic state is induced.

In *hysteria* a similar cortical discharge is assumed to take place.

Reflex convulsions are common in childhood as a result of digestive disturbance, intestinal worms, etc.

Tremor.—The pathological cause of tremor is absolutely unknown, and so far unexplained; it is of nervous origin, and is due undoubtedly to a disturbance of the normal innervation currents passing from the spinal motor neurones to synergic groups of muscles, whether these are in action or in passive tonic contraction. But we know that the innervation currents flowing out of the anterior roots to synergic groups of muscles are not automatically generated in the anterior horn cells of which they are projections, but are generated under the influence of innervation currents flowing from the cerebrum and cerebellum, and reflexly through the posterior roots. A functional or organic disturbance of the nervous structures which regulate and adjust the outflow of the innervation currents from these spinal motor neurones would serve as a cause of tremors. Indeed, we know that in disseminated sclerosis focal lesions of the middle peduncle, the corpora quadrigemina, and other structures of the mid-brain, may occasion *nystagmus,* which is a form of tremor. Again, experience has shown that tremor is one of the most persistent results of cerebellar lesions, when a movement is voluntary executed. But it must be remembered that in agenesis of the cerebellum no such effects are observed, consequently we must regard tremors in cerebellar lesions as a result of disturbance of functional correlation rather than of actual loss of cerebellar function.[1]

Malformations of the Central Nervous System.

The brain and spinal cord are subject to a number of malformations. The cerebrum and part of the cerebral axis may be wholly or partially deficient (total or partial *anencephalia*) and may be associated with total or partial absence of the cranial vault (*acrania* or *hemicrania*) or imperfect closure of the skull along the middle line (*cranioschisis*). Similar conditions may occur in the spinal cord and vertebral column. When the defect mainly affects the anterior part of the fore-brain there may be but a single central eye (*cyclopean monster*), etc.; in other cases, if the defect is slight, hare-lip, cleft-palate, etc., result. Fissures of the cranial bones are frequently associated with protrusion (hernia) of the brain, *encephalocele,* or if the membranes only protrude, *meningocele.* If this condition obtains in the vertebral canal, it is termed *myelomeningocele,* or spinal *meningocele.* This is known as *spina bifida,* is commonest in the lumbo-sacral region, and the bony vertebral arch may be more or less deficient. An increased quantity of fluid may accumulate in the ventricles or medullary tube, *congenital internal hydrocephalus,* in the subarachnoid tissue, *meningeal hydrocephalus,* or in the central canal of the cord, *hydromyelia.*

When the brain is smaller than normal this condition is known as *microcephaly,* the gyri and sulci are, as a rule, ill-developed and abnormal in arrangement, and it is frequently associated with premature ossification of the cranial sutures.

Hypertrophy of the brain, *macrocephaly,* is also occasionally observed. The cerebral substance may be in excess, but hyperplasia of the neuroglia is generally present.

DISORDERS OF THE CIRCULATION AND VESSELS.

The amount of blood contained in the vessels of the cerebro-spinal system is subject to considerable physiological variations. During activity, especially mental activity, the cerebral vessels are dilated; during rest and sleep the brain is comparatively anæmic.

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[1] See Mott, *The Practitioner,* Sept., 1902, p. 293.

ACTIVE OR ARTERIAL HYPERÆMIA, or congestion, may occur when the heart is hypertrophied or its activity increased, but is not of great moment. It may occur locally in connexion with new growths, tubercle, syphilis, or focal inflammation.

PASSIVE HYPERÆMIA, or engorgement, occurs in chronic heart disease, etc., when the return of venous blood is obstructed. Local engorgement may be due to thrombosis, pressure of tumours, etc.

ANÆMIA is met with in general anæmia, or in contraction or morbid thickening of the arteries. It is usually local and then due to thrombosis or embolism, pressure, etc.

HÆMORRHAGE is particularly liable to occur in the brain, usually by rupture, occasionally by diapedesis. Capillary or punctate hæmorrhages result from degenerative changes in the vessels, thrombosis or embolism, inflammatory conditions, traumatism, and extreme venous engorgement, such as may occur during convulsions, are commoner in the grey than in the white matter, and appear as round or oval spots, in size varying from minute points up to a pea, often mottling the cut surface. They may be absorbed without leaving any trace.

Extensive spontaneous hæmorrhage is known as *apoplexy*. This results from the rupture of an artery, and takes place only when the vessel-wall has lost its normal power of resistance owing to degeneration or inflammatory changes, aneurysmal dilatation not infrequently preceding the rupture. Increased arterial pressure, such as accompanies the hypertrophied heart in renal cirrhosis and arteriosclerosis, emphysema, coughing, and straining, are frequent predisposing causes, but are operative only when the vessel-walls are diseased; a normal vessel will withstand any increased pressure to which it may be subjected, except perhaps in the very young if subjected to extreme violence, as during convulsions. Hæmorrhage occurs most commonly into the basal ganglia and internal capsule, particularly the latter, less commonly into the pons, crura, and cerebellum, rarely on the convexity of the hemispheres. This distribution depends on the distribution of arterial pressure, which is highest in the Sylvian artery supplying the basal ganglia and internal capsule. Only when the hæmorrhage is of the smallest dimensions can the nerve-tissues escape injury; when it is of any size the nerve-tissues must be more or less compressed and lacerated. The primary effect of the effusion of blood is to cause shock and insensibility, after which, if the immediate injury be recovered from, various disturbances of function, dependent on the seat of the lesion, will be manifest. The commonest result is a hemiplegia on the side opposite the lesion, the face escaping to a large extent but not entirely, and sensation being but slightly affected. This happens when the hæmorrhage is into the anterior two thirds of the posterior half of the interior capsule; if the posterior portion be involved, more or less anæsthesia will be present in addition. Hæmorrhage into the pons will produce the so-called "crossed paralysis," paralysis of the face on the same side as, and of the body on the side opposite to, the lesion. This is owing to involvement of the third, fourth, sixth, and seventh nerves in addition to the motor tract.

A recent hæmorrhage forms a dark red pulpy mass containing fragments of disintegrated nerve-tissue, and if large may cause anæmia of the rest of the brain and flattening of the convolutions. In hæmorrhage on the surface of the brain from the meningeal arteries the extravasated blood spreads out, coagulates, and forms a thin layer over the cortex.

When the blood coagulates the clot contracts, and the expressed serum is absorbed by the blood-vessels and lymphatics; the colour then becomes a reddish brown. As time goes on leucocytes invade the mass, the hæmoglobin is to a large extent removed, and a contracted scar, perhaps rusty in colour, is all that remains, an *apoplectic cicatrix.* In other cases, the detritus having been absorbed, the space occupied by it becomes filled with fluid, an *apoplectic cyst.*

Embolism and thrombosis are also very common in the cerebral vessels. Embolism usually results from aortic or mitral cardiac disease, vegetations becoming detached and being carried to the cerebral vessels. Thrombosis is frequent when the cerebral vessels are diseased, as in arteriosclerosis and syphilis. In both cases it is the Sylvian artery and its branches which mainly suffer, more often the left than the right, and chiefly the branches supplying the internal capsule. Next in frequency come the arteries supplying the cortex, the middle, posterior, and anterior cerebral arteries in this order. The results are much the same as in cerebral hæmorrhage, but the lesion is not usually so severe, and there is a better chance of recovery than in the latter, while shock and insensibility are less marked or absent. Disturbance of function occurs, as in hæmorrhage, and is dependent on the seat of the lesion. A characteristic combination of symptoms is right hemiplegia with motor aphasia, which is a sequel to blocking of the left middle cerebral artery, which supplies the posterior part of the third left frontal (or Broca's) convolution, which is the motor centre for articulation.

If necrosis follows rapidly on the occlusion of the vessel, all that will be seen is an anæmic area corresponding with the distribution of the vessel, with a certain amount of surrounding venous engorgement. More generally *softening* ensues, and may be red, white, or yellow.

In white softening, after the occlusion, a certain amount of serum but no blood-corpuscles passes from the vessels and saturates the necrotic area, which becomes soft and semi-fluid—*i. e.* there is a non-hæmorrhagic infarct. In red softening more or less blood extravasates from the veins and capillaries, a condition of hæmorrhagic infarction being present. If the occlusion slowly develops and the tissues are gradually deprived of their nutriment, slow degeneration ensues, with conversion of the myelin into a granular substance, with fatty particles; this is known as grey softening.

Yellow softening is generally a late stage in the red, the blood-colouring matter having been absorbed and fatty degeneration having followed.

A cellular infiltration may subsequently surround the affected area and a process of cicatrisation ultimately ensue. The changes in the nerve elements are characterised by a varicosity of the processes of the ganglion-cells, chromatolysis of the bodies of the ganglion-cells, and atrophy of the axons.

Many infantile cerebral palsies may be due to rupture or occlusion of cerebral vessels, which may take place, not only at birth and following it, but also during intra-uterine life.

Multiple and widespread thromboses of the smaller vessels sometimes occur, leading to a form of softening which has been termed *Parrot's disease.* The ætiology is unknown.

Thrombosis of the large venous sinuses of the dura, the lateral, longitudinal, etc., is generally of septic origin and secondary to ear or mastoid disease, disease of the cranial bones, meningitis, etc.

Hæmorrhage into the spinal cord (spinal apoplexy, hæmatomyelia) is far less common than cerebral apoplexy, and is almost always situated in the cervical region and in the grey matter. In traumatism, of course, the hæmorrhage may be in any region.

Œdema of the brain and cord occurs as a result of engorgement in chronic cardiac and lung diseases, cardiac failure and paralysis, and the so-called hydræmic dropsy in nephritis. Local œdema of engorgement is common round hæmorrhages, thromboses, and tumours, and in cases of acute hydrocephalus sometimes occurs in the region of the internal capsule, producing transient hemiplegia. Inflammatory œdema occurs in the neighbourhood of inflammatory foci, and occasionally around patches of softening and tumours, in the meninges as a result of meningitis, and in the ventricles and central canal of the cord from inflammatory changes in the vessels of the plexuses and ependyma.

Acute congestive œdema is said to occur as the result of sudden cerebral engorgement, a rise in the intracranial blood-pressure producing compression of the vessels and obstruction to the outflow of blood from the meninges, whereby secondary engorgement and œdema are produced.

Owing to the structure of the central nervous system, the dropsical fluid mostly accumulates in the large lymph-spaces about the sheaths of the pial vessels, the subarachnoid and pial spaces, the ventricles, and central canal of the cord. We may thus have meningeal dropsy or *external hydrocephalus*, ventricular dropsy or *internal hydrocephalus,* and dropsy of the central canal or *hydromyelia.* In most cases of cerebro-spinal dropsy the fluid partakes more or less of the characters of cerebro-spinal fluid—*i. e.* it contains a reducing substance and but little proteid.

In meningeal dropsy the sulci become widened, in ventricular dropsy the convolutions become flattened, the membranes stretched, and, if occurring before the sutures have ossified, the cranial bones separate, and the skull enlarges. The membranes are frequently thickened, and cystic spaces may form through inflammatory adhesions and cysts develop in the choroid plexuses.

Hydrocephalus may be acute or chronic, congenital or acquired, and external or internal. The commonest form of acute hydrocephalus is inflammation of the pia mater if external, of the ventricular pia and choroid if internal; while compression of the tela obstructs the veins of Galen and further increases vascular engorgement and exudation; in the adult it is almost always due to subtentorial tumour compressing the veins of Galen, the outlet from the lateral ventricles, or both of these. The ætiology of congenital hydrocephalus is uncertain, but it may be caused by inflammation of the ependyma during intra-uterine life, or to mal-development. In extreme cases of hydrocephalus the head may be enormously enlarged, particularly antero-posteriorly (*dolichocephalic*), the convolutions and sutures obliterated, and the cerebral substance covering the distended ventricles may be so stretched as to become as thin as cardboard. The face is small, the forehead bulging and overhanging, and optic neuritis with subsequent atrophy may occur and lead to blindness.

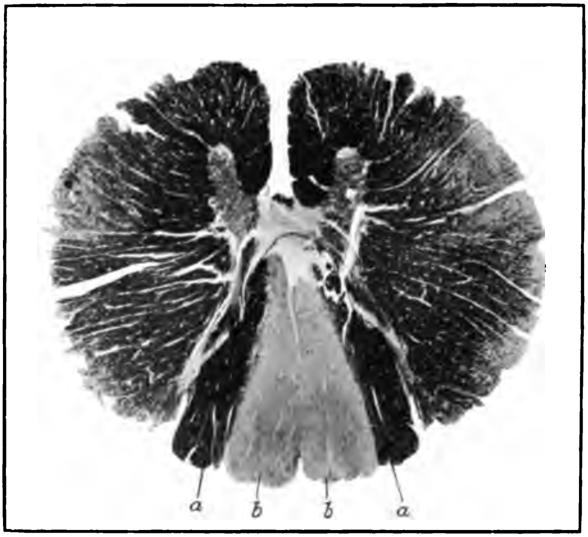
Syringomyelia, which may conveniently be considered here, is a term applied to a disease of the cord characterised by the formation of cavities or holes in its substance, surrounded by an excess of neuroglia tissue, and accompanied by various motor, sensory, and trophic disturbances. The cavitation is usually single, and is a new formation and thus distinguished from hydromyelia, in which the central canal is distended, and which may accompany syringomyelia.

Various theories have been advanced to account for this remarkable condition. One is that there is first a new growth of neuroglia tissue owing to proliferation of the ependyma cells, and also of the epithelium lining the central canal. This is followed by vascular changes, degeneration of the vessels, thrombosis, embolism, and hæmorrhage, subsequent degeneration of the new neuroglia tissue with absorption, and the formation of a cavity (gliasis). Another view is that it is developmental in origin; embryonal neuroglia tissue, which should have undergone transformation, proliferating, and by compressing itself and the neural elements around, degeneration and cavitation ensue. A third theory suggests that the process is inflammatory throughout, a periependymal myelitis. As regards ætiology nothing is known; trauma has been advanced as a cause and might induce hæmorrhage, which, by becoming encysted and surrounded by gliomatous degeneration, suggests another mode of origin.

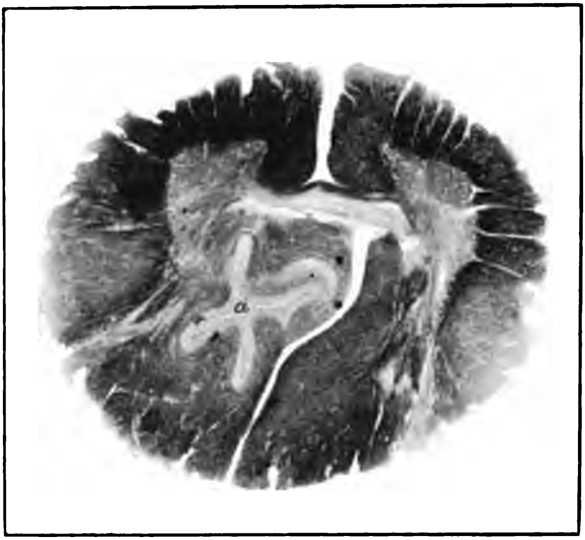
The form and extent of the cavity or cavities vary. The shape is often irregular or angular, and the contents may be either a clear fluid or a hyaline jelly (Plate XXVI., B.). The cavities are smooth and lined with a tough membrane, consisting of proliferated and compressed neuroglia tissue. Various degenerative changes in the white and the grey matter accompany the condition.

One form of syringomyelia, known as Morvan's dis-

PLATE XXVI.



A. Degeneration ascending from a transverse lesion of the cord. Secondary degeneration is seen in the postero-median (Goll's) columns (*b*, *b*), also in the antero-lateral ascending and direct cerebellar tracts. Burdach's columns (*a*, *a*) are unaffected. (Weigert-Pal, × 6.)



B. Syringo-myelia of cord from tumour formation. Note the cystic space (*a*), distortion of the cord, and degeneration in the crossed pyramidal tracts. (Weigert-Pal method, × 6.)

ease, in which panaris is a striking clinical feature, has been suggested as being a manifestation of leprosy, but this seems unlikely.

AFFECTIONS OF THE MEMBRANES.

Anæmia may occur in general anæmia. Hyperæmia occurs in the early stages of inflammation, and is associated with tumours, gummata, and other focal diseases, and in the spinal cord by extension from without. Passive hyperæmia accompanies general venous stasis, and in the brain, thrombosis of the venous sinuses. Hæmorrhages are met with in scurvy and purpura, and particularly in traumatism. Hæmorrhages are more commonly extra-dural, in the brain due to fracture of the skull, in the cord to vertebral fracture, the rupture of an aneurysm, etc. Extravasation into the substance of the cerebral dura is occasionally associated with extra-dural hæmorrhage, and has been described as "Pott's puffy tumour."

Inflammation.

The membranes of the brain and spinal cord are the subject of various forms of inflammation, which is known generically as *meningitis*. When the cerebral meninges are alone affected the term *meningitis*, without qualification, is employed; when the spinal meninges are the seat of inflammation the condition is known as *spinal meningitis*. Meningitis is far commoner than spinal meningitis, and the latter, when it occurs, is frequently an extension from the former, or is associated with local disease. The inflammation may be acute or chronic. When the dura mater is affected it is known as *pachymeningitis*, when the pia-arachnoid the term *leptomeningitis* is applied.

Pachymeningitis may be external or internal, according as the external or the internal surface of the dura is affected. The former, whether of the brain or of the spinal cord, is almost always associated with injuries or diseases of the bones, and is unimportant. Internal pachymeningitis may be (1) hæmorrhagic, (2) suppurative, (3) tuberculous, or (4) syphilitic.

Hæmorrhagic pachymeningitis is more frequent in the aged than in the young, and is not uncommon in the insane and in degenerative diseases of the brain. Alcoholism and trauma seem to be ætiological factors in its development. At an early stage the inner surface of the dura will be found to be lined with a thin membrane of delicate connective tissue, which leaves a number of bleeding points on endeavouring to separate it. Sometimes there is an appearance as of patches of ecchymosis. Later the dura becomes tough and thickened, greyish-red, and more or less adherent in places, in others lined with blood-clot in various stages of coagulation and disintegration, sometimes presenting a lamellated appearance, owing to successive hæmorrhages. Microscopically, there is round-celled infiltration of the dura, with the formation of immature connective tissue and blood-vessels. The condition is generally regarded as inflammatory in origin, but has also been stated to result from primary hæmorrhage, with consecutive membrane formation.

The seat of the disease is most frequently over the vertex, but it may also occur in the frontal and basal regions, and rarely in the spinal dura, particularly in the cervical region (*hypertrophic cervical pachymeningitis* of Charcot).

Suppurative pachymeningitis occurs in connexion with disease of the bones, septic thrombosis of the venous sinuses, and rarely by extension from a leptomeningitis. The dura is thickened, reddened, and swollen and softened, infiltrated with cells, and an inflammatory exudation or occasionally pus coats the surface of the membrane.

Tuberculous pachymeningitis is rare, and occurs only in connexion with tuberculous leptomeningitis.

Syphilitic pachymeningitis is usually associated with syphilitic leptomeningitis and encephalitis, and is especially met with in general paralysis of the insane. It consists of a cellular infiltration of the dura, particularly about the vessels, which show a syphilitic endarteritis. The dura becomes thickened, tough, and whitish, and more or less attached to the cranial vault on the one side and to the pia-arachnoid on the other, and osseous plates often develop in the thickened membrane. Gummata are also frequent in the dura.

THE PIA-ARACHNOID.—The pia mater is a vascular membrane consisting of two layers. The inner or visceral layer is in intimate contact with the brain and cord, dipping into the fissures, and sending prolongations around the vessels entering the substance of the brain and cord, which constitute the perivascular lymph-spaces. The external or parietal layer of the pia, frequently described as a distinct membrane, the arachnoid, loosely covers the visceral layer, not dipping into the fissures, and between the two layers there is thus a space, the pial space (or subarachnoid space), which is divided into numerous compartments by bands of fibrous tissue passing from one layer to the other (the pial space of the cord is not so divided). The pial space is practically a large lymph-sac filled with the cerebro-spinal fluid, and divided by the connecting bands of fibrous tissue between the two layers into sinuses, or *cisterns.*

The largest of these lymph-sacs lies around the medulla and on the lower surface of the cerebellum, and is named the "cisterna magna cerebello medullaris." From this huge sac there run forward over the pons mainly three other sacs. These are named from their positions respectively "cisterna medialis pontis," and the two "cisternæ laterales pontis." The former surrounds the basilar artery, and is flanked on either side by a lateral sac. The medial sac passes forwards to end in a blind extremity. Another sac occupying the middle line in front of these is the "cisterna chiasmatis." It lies underneath the optic chiasma, and is richly beset with trabeculæ. Passing out from this on either side are the two large "cisternæ fossæ Sylvii," diverging into the two Sylvian fossæ and receiving tributaries from the subarachnoid spaces of the neighbouring sulci (Hamilton).

These cisterns communicate with the fourth ventricle through the foramen of Majendie, with the lateral ventricles through the foramina of Luschka, and on the convexity of the brain with the longitudinal sinus through the Pacchionian bodies. There is no communication between the pial space and the subdural space (between the dura and the arachnoid); this empties into the jugular lymphatic plexus. The lymph-spaces of the brain and cord are practically continuous, and the pial spaces of the cord empty into the cisterns at the base of the brain, the central canal into the fourth ventricle. The flow of cerebro-spinal fluid is from the lateral ventricles through the foramen of Munro into the third ventricle, thence through the aqueduct of Sylvius into the fourth ventricle, and through the foramina of Majendie and of Luschka into the cisterns at the base of the brain. These anatomical and physiological facts are of importance in the pathogenesis of meningitis, and of certain forms of hydrocephalus.

LEPTOMENINGITIS.—This is the most frequent and important variety of meningitis, and is the usual form of inflammation to which the term is applied clinically. It may be acute or chronic and serous or purulent. The tuberculous and syphilitic varieties are of considerable pathological importance. *Acute serous leptomeningitis* occurs in infancy and childhood, and consists in a sudden congestive hyperæmia, followed by effusion into the pial spaces, either externally (external hydrocephalus), or internally into the ventricles (internal hydrocephalus). The convolutions become flattened, the ventricles dilated, and the choroid plexuses are hyperæmic. The fluid is clear or slightly opalescent, and contains minute flakes of fibrin, a few pus-corpuscles, and more proteid than normal. There is frequently a coincident superficial encephalitis, with a sero-cellular infiltration of the grey matter and degeneration of the ganglion-cells. Occasionally the external form may be sharply circumscribed, so that a sub-arachnoid cyst is formed. This variety of meningitis sometimes occurs in the course of infective diseases such as measles and scarlatina. In those addicted to the immoderate use of alcohol a somewhat similar condition is met with. The pia and brain substance are œdematous, and the name "wet brain" aptly describes the appearances seen. There is a cellular infiltration of the meninges, exudation from the vessels, and degeneration of the cortical cells. These changes explain the psychical symptoms and meningeal irritation so often met with in alcoholics.

Purulent leptomeningitis is the commonest variety and is always infective. It is much more frequent in the brain than in the cord, but may extend from the former to the latter, and in exceptional instances the whole nervous system may be involved. Occasionally the condition may arise in connexion with wounds or disease of the skull or spine, especially chronic ear or mastoid disease, rarely in the course of pyæmia, or secondary to a cerebral abscess. In these cases the infective micro-organisms are usually staphylococci or streptococci.

Most frequently this form of meningitis occurs sporadically or in epidemic form, and is due to either the *Diplococcus pneumoniæ* (some 60 per cent. of the cases) or the *Diplococcus intracellularis*. In tuberculous meningitis there is first an eruption of tubercles, subsequently followed by the formation of a serous, sero-fibrinous, or purulent exudation. In the mild cases there may be slight redness and œdema of the parietal pia, with an increase of fluid containing fibrinous flakes in the pial space along the cerebral fissures. In more marked cases the pial space may be distended with a semi-purulent or purulent fluid, greenish-yellow in colour, viscid, and tenacious; this is rarely found on the dural surface of the pia. Microscopically, the blood-vessels of the pia are dilated and filled with corpuscles and surrounded with collections of round cells, mostly polymorphonuclear leucocytes. Sometimes the veins are crowded with leucocytes or plugged with coagula. The cortex may be almost unaffected but the inflammation frequently spreads along the pial sheaths and it becomes œdematous and the ganglion cells swollen and degenerate. If the cord be involved the axis cylinders may be swollen and partially disintegrated, with degeneration of the medullary sheaths and nerve-roots.

The inflammation and exudation may be most abundant at the base of the brain, but often may cover the whole surface and extend into the ventricles.

In epidemic cerebro-spinal meningitis, sporadic cases of which are occasionally seen in London, but which may occur in serious outbreaks, much the same changes are present, but the meninges of the whole cerebrospinal system may be simultaneously attacked, or the condition may predominate in the cord, but is usually most marked at the base of the brain and posterior surface of the cord. The organism causing it, the *Diplococcus intracellularis* of Weichselbaum, occurs as a small diplococcus within the leucocytes and pus-cells, and is decolourised by Gram's method of staining, in these respects resembling the gonococcus, but distinguished from the latter by its free growth as a creamy layer on agar at blood-heat. It hardly grows at room temperature.

The gonococcus has also been found to be the cause of a cerebro-spinal meningitis in a few instances. The colon, the typhoid, and possibly the influenza bacillus may also cause a leptomeningitis.

A variety of the disease has been described under the name "posterior basal meningitis of infants" by Gee, Carr, and others. It attacks infants, usually between the third and twelfth months, and is curiously limited to an area of the brain extending from the optic commissure to the lower end of the medulla, over which region the pia-arachnoid is much thickened, and the parts are matted together. A diplococcus has repeatedly been isolated by Still which is probably a variety of the *Diplococcus intracellularis*.

Chronic leptomeningitis may result from the acute form, or may be chronic from the first, and is then usually associated with encephalitis. There is thickening and opacity of the pia, often patchy, owing to an extensive fibrous hyperplasia with adhesions to the brain and skull, located chiefly in the anterior portion of the hemispheres. Its causation is obscure, but trauma, sunstroke, alcoholism, and syphilis may play a part. In some instances it probably starts in the cortex and spreads to the pia.

Syphilitic leptomeningitis has its favourite seat at the base of the brain, especially in the middle fossa, next in the frontal and parietal lobes. Gummata are most frequent in the interpeduncular space. The changes are much the same as in the chronic form, and in addition the vessels are more or less affected with a syphilitic endarteritis.

Syphilitic leptomeningitis is frequently associated with pachymeningitis and encephalitis, the condition being known as meningo-encephalitis, such as is met with in general paralysis of the insane.

MENINGEAL TUBERCULOSIS.—Tuberculosis usually manifests itself in the basal cerebral pia, rarely in the dura, and is then an extension from the pia, and very rarely in the spinal pia. It occurs mostly in young children, and is nearly always secondary to tubercle elsewhere.

It is generally seen as an eruption of miliary tubercles, which appear as whitish spots, from a pin-point to a pin's head in size, along the course of the vessels, principally in those of the processes of the pia, which dip into the Sylvian fissure in the spaces at the base of the brain—*e. g.* around the optic chiasma and the anterior and posterior perforated spaces, and in the vessels forming the circle of Willis. In addition to the tubercles, there is a serous, sero-fibrinous, or semi-purulent exudation, varying in amount from a mere moistness or deposition of flakes of lymph to a considerable quantity, distending the ventricles and "cisterns," and causing flattening of the convolutions. The cortex is reddened, swollen, and œdematous, and the veins of the diplöe and sinuses of the dura are distended with blood.

Occasionally the tubercle bacilli lodge in a single branch of the meningeal vessels, and the localised eruption of tubercles resulting therefrom coalesce to form a single caseous mass, which may be as large as a walnut; to this form the name of *solitary tubercle* is applied.

TUMOURS of the dura are not infrequent, chiefly sarcomata of an alveolar, angeio, or round-celled type. Endotheliomata, fibromata, and psammomata also occur, and occasionally carcinoma, either as an extension from adjacent parts or by metastasis.

In the pia the Pacchionian bodies are frequently enlarged, forming small nodules, chiefly along the upper edge of the superior longitudinal sinus, consisting of dense masses of fibrous tissue covered by several layers of endothelium, which gives them a concentric structure. Endotheliomata also occur.

DISEASES OF THE BRAIN.

Encephalitis, inflammation of the brain substance, more particularly of the grey matter, may be acute or chronic, and the cerebrum is more frequently affected than the cerebellum, while the pons, crura, and medulla are rarely involved.

Acute hæmorrhagic encephalitis may be focal or more or less diffuse, and occurs in the course of infective diseases, such as typhoid, diphtheria, influenza, etc., principally in the motor area of the cortex, sometimes in the temporal lobes and corpus striatum. The blood-vessels are primarily involved; there is intense hyperæmia, hæmorrhagic exudation and leucocytic infiltration, and multiple small hæmorrhages, and the ganglion cells are degenerate. The membranes may be inflamed and the affected patches of the cerebral substance are reddened, swollen, and softened. Occasionally extensive hæmorrhages may occur.

In the course of certain toxæmias, chronic alcoholism, lead, etc., the stress of the process may fall on the grey matter of the floor of the third ventricle and aqueduct of Sylvius. This variety has been termed *acute poliencephalitis superior.*

Acute suppurative encephalitis is generally seen as a circumscribed affection, or cerebral abscess. The causes are trauma, middle-ear disease (some 35 per cent. of the cases), disease of the frontal and ethmoidal sinuses, and in connexion with pyæmic processes in other parts of the body. The ætiological organisms are usually either the *Staphylococcus aureus,* the streptococcus, or the *Diplococcus pneumoniæ,* occasionally others.

Abscess of the brain is generally single, and is more common on the right side; if arising in connexion with ear disease, it is generally on the same side as the lesion, and is situated most frequently in the temporo-sphenoidal lobe or cerebellum; if from trauma, it is often superficial; if pyæmic, it frequently develops in the area supplied by the left Sylvian artery. If the abscess form rapidly, it is hardly encapsuled, the wall being composed of the *débris* of brain-tissue, but if it be chronic a more or less definite membrane limits its boundaries. If it be situated in the cortex, more or less purulent leptomeningitis accompanies it, and the inflammation may spread to the dura and involve the venous sinuses, producing septic thrombosis.

The results of an abscess are various. There will be the usual accompaniments of septic infection and motor and sensory lesions depending on the situation and direction of the pressure; but if development be slow and chronic, the symptoms may sometimes be strangely masked and inconspicuous. An abscess of any size will produce bulging and flattening of the convolutions in its neighbourhood, and there may be affection of the bones, extra-dural collections of pus, purulent meningitis, with sometimes hæmorrhagic encephalitis in other parts of the brain.

Chronic encephalitis may be diffuse, limited, and circumscribed, or occur as multiple scattered patches. Its pathology is obscure, but it may result from an acute encephalitis, may surround a chronic abscess, or may develop in connexion with tuberculous disease or syphilis. In the form of multiple scattered patches it is seen in Huntingdon's chorea, in multiple sclerosis, and in general paralysis of the insane. The white matter is the principal seat of change; the neuroglia undergoes hyperplasia with the formation of dense masses of fibrous tissue—sclerosis. The changes commence in the neighbourhood of the vessels, and subsequently the ganglion-cells become atrophied as a result of pressure. The involved areas become contracted, the convolutions smaller, and the sulci broader, and the consistency of the tissues is increased and may be almost cartilaginous.

In *Huntingdon's chorea* the cortex of the frontal and central regions of the brain is mainly involved. In *multiple sclerosis* (insular or disseminated sclerosis) there are foci of neuroglial hyperplasia, with degeneration of the myelin sheaths, but not to a great extent of the axis cylinders, scattered throughout the central nervous system, in the cortex, especially in the neighbourhood of the lateral ventricles, in the pons and medulla, and in the cervical and lumbar enlargements of the cord (Pl. XXVIII., A.). These appear as greyish or shining points, varying in size from a pin's head up to a walnut. The walls of the blood-vessels are usually thickened, and in the involved areas there is some round-celled infiltration. The pia in the neighbourhood of the sclerotic patches is often thickened and adherent. In some cases there may be little true neuroglial hyperplasia, the sclerosis arising from newly-formed connective tissue.

The pathology of this disease has been the subject of much discussion; some have regarded it as a primary degeneration, others as inflammatory; some have considered it to be a primary disease of the neuroglia, others that it commences in the perivascular spaces, subsequently involving the surrounding tissues, and this seems more likely to be the correct view.

Little is known of the ætiology of multiple sclerosis. It has been regarded as toxæmic; in certain instances, particularly in those in which there is much neuroglial hyperplasia, it may be due to some defective embryonic development. Since the axis cylinders, for a long time at least, escape destruction, there is no secondary degeneration until late in the course of the disease.

In *general paralysis*, as already stated, there are generally changes in the meninges. The dura is often adherent and the seat of an internal hæmorrhagic pachymeningitis, particularly over the convexity, and the pia is cloudy and thickened. The convolutions are often flattened, the brain pale, the ventricles enlarged, and the choroid plexuses the seat of granulations. Microscopically, there is first swelling and cloudiness of the ganglion-cells, followed by degeneration of the nucleus, granulation, and atrophy, particularly in the cortex of the frontal region, the myelin sheath of the white fibres is more or less disintegrated, there is considerable neuroglial hyperplasia with increase in the number of nuclei, and increase in the connective tissue of the pial prolongations. In addition there is marked degeneration of the blood-vessels, thickening of their walls, and proliferation in the adventitia, and a marked perivascular infiltration in which plasma-cells are usually abundant. These changes are always most marked in the cortex, but also occur in the basal ganglia, medulla, and pons, and in the posterior columns of the cord. The condition has been regarded as being essentially a meningo-encephalitis, probably starting in the ganglion cells and spreading thence to the neuroglia and connective tissue. Whether it is really an inflammation or a primary degeneration has been disputed. Its essential causation is now regarded as being due to syphilis. The amount of cerebro-spinal fluid is increased in cases of general paralysis, it is richer in solids, and choline is present in it and in the blood in appreciable amounts (see p. 477).

Much the same changes are met with in *sleeping sickness*, but the base of the brain is more affected than the cortex, and there is less neurone-destruction and glia-proliferation than in general paralysis.

The perivascular canalicular systems are filled with large and small mononuclear leucocytes, trypanosomes are difficult to detect, and a diplococcal infection is nearly always present.

Tumours of the brain, other than tubercle, gumma, and parasitic cysts, are usually glioma or sarcoma. Osteoma may develop from the cranial bones; carcinoma, fibroma, psammoma, and cholesteatoma and aneurysm are occasionally seen.

The *glioma* develops from the neuroglia tissue of the central nervous system, and is most frequent in the young. Being very vascular, it appears as a pinkish or reddish mass, usually somewhat harder in consistence than the tissue from which it springs. Microscopically, it consists of neuroglia tissue, rich in nucleated cells with long protoplasmic processes ramifying in every direction, and permeated with capillaries and small, thin-walled vessels.

Sarcoma is more frequent in adults, and develops from the connective tissue of the pia or blood-vessels or from the bones. It is generally of the round- or spindle-celled type.

Cholesteatoma is a tumour of rare occurrence containing cholesterin surrounded with laminated layers of squamous cells. It is more frequent in the meninges than in the brain.

Psammoma is a tumour containing calcareous granules, and mostly found in the choroid plexus and membranes.

Echinococcus cysts are not infrequent in the brain in Australia, Central and Southern Europe, and Iceland. In sheep they are common, causing the disease known as "staggers."

The Choroid Plexus.

The choroid plexus is a plexus of vessels developed from the mesoblast and covered everywhere with a layer of cubical or columnar epithelium. It is probably the main secretory organ of the cerebro-spinal fluid. In some cases a hypersecretion of fluid may take place, and if a communication with the nose is established through the ethmoid, as in a case described by StClair Thomson, there may be a discharge of cerebro-spinal fluid through the nose.

The choroid plexus is frequently the seat of inflammation and of tubercle, secondary to similar affections of the meninges. Calcification may be present in it, and cysts, endotheliomata, and epitheliomata also occur.

The PITUITARY BODY is discussed at p. 215.

DISEASES OF THE SPINAL CORD.

Hyperæmia, active and passive, and anæmia occur in the cord under the same circumstances as they do elsewhere. Hæmorrhage in a massive form is always the result of traumatism or the rupture of an aneurysm. Punctate hæmorrhages may be met with in infective diseases, especially in tetanus and hydrophobia.

Diseases of the blood-vessels are similar to those occurring in other parts of the body. Hyaline degeneration of their walls is common, particularly in sclerosis, and is generally present to some extent in the cords of persons dying after middle-life. An endarteritis and periarteritis, with perivascular insular scleroses, and some degeneration in the lateral and posterior columns, have been suggested as the anatomical basis of paralysis agitans, but these changes do not seem to be constant.

Lardaceous degeneration occasionally occurs in general lardaceous disease. It must be distinguished from an artificial condition resembling it, often noticed in cords preserved in spirit.

Inflammation.

MYELITIS, inflammation of the cord, has been applied to any form of softening, even to that due to compression, which, however, is hardly an inflammation, but is due to the mechanical interference with the vascular and lymph circulations with consecutive œdema and softening.

Acute myelitis may be localised, transverse, or diffuse. It may involve more or less of the cord in a particular segment, or a short portion of its length (transverse myelitis); it may occur in multiple foci (disseminated myelitis), or may be confined to the grey matter (poliomyelitis).

As regards ætiology, cold and chill often precede the attack, but are probably merely predisposing factors, the essential cause being toxæmic or infective. Occasionally it is due to an extension from a meningitis. It may be apparently primary or may be secondary to gonorrhœa and other infective diseases. The part played by syphilis is uncertain.

In a spinal cord affected with myelitis the amount of cerebro-spinal fluid is often increased, the pia over the inflamed area is reddened from congestion, and the area of softening has lost its normal elastic consistence and feels pultaceous. On section, the softened area may be semi-fluid, the normal markings are lost, and if hæmorrhage has occurred, the colour will be reddish or chocolate-brown. Microscopically, the substance of the cord is disintegrated, the vessels are dilated, round cells (many of which are markedly granular) have accumulated in the perivascular lymph-spaces and infiltrate the tissues, and myelin and fat globules are present. The myelin sheaths and axis cylinders of the white fibres suffer; the former are more or less degenerate and broken up, the latter are swollen, granular, sometimes beaded and tortuous. The ganglion-cells are swollen and degenerate, the nucleus stains badly, and the Nissl granules disappear. The neuroglia-cells may be swollen and increased in number; if the process be chronic, neuroglial hyperplasia may be present. Above and below the lesion ascending and descending degenerations will be present.

So-called trophic lesions accompany the disease, wasting of muscles, bed-sores, and cystitis and pyelitis from paralysis of the bladder. Occasionally suppuration may occur, and an abscess form in the cord.

In hydrophobia, a considerable leucocytic exudation surrounds the vessels (the "rabic tubercle" of Babes), particularly in the grey matter, both in the upper part of the cord and in the medulla, and the ganglion-cells of the superior cervical ganglion are shrunken and atrophied, and do not nearly fill their capsules (van Gehuchten).

After a myelitis such nerve-fibres and ganglion-cells as are not hopelessly damaged recover, but there is no new formation of these elements; so that, unless the process has been slight and circumscribed, complete recovery hardly ever ensues, a certain amount of paralysis, rigidity, and muscular atrophy remaining. Recovery in any case is slow, occupying many months, but it is often astonishing to what an extent it takes place. A good deal of neuroglial hyperplasia may succeed the acute process.

The changes resulting from slowly developing pressure—*e.g.* from a tumour or tuberculous disease of the spine—are much the same as those described above, but not so severe, the grey matter being affected less than the white, and apparently the nerve elements, owing to the gradual nature of the process, become accustomed to the pressure and suffer less than when the process is acute, so that considerable compression may be completely recovered from.

Acute anterior poliomyelitis, the so-called infantile paralysis, is a disease almost exclusively confined to children, and though often developing after exposure to cold or subsequent to measles, etc., is almost certainly infective in origin, but no specific organism has yet been isolated. The ganglion-cells of the anterior horns of the grey matter are mainly affected, causing atrophy of the muscles supplied by them. The invasion is usually acute and accompanied with fever.

In recent poliomyelitis the pia is congested, the cerebro-spinal fluid increased in amount, and small areas of the cord will be found to be less resistant than normal. Microscopically, most of the ganglion-cells of the anterior cornua will be found to be affected, the extent of the lesion varying from a condition of swelling, vacuolation, and chromatolysis to a complete disintegration and shrinking, the disintegrated cells being surrounded with a round-celled infiltration (Pl. XXVII., A.). The blood-vessels are distended and the perivascular spaces are filled with round cells. The non-medullated fibres of the anterior horn are swollen, and the neuroglia tissue proliferating, and the white matter in the neighbourhood of the inflamed areas also shows inflammatory changes. In old cases of poliomyelitis the cord is shrunken in the affected areas, and on section the shrunken outline of the anterior horn is plainly visible to the naked eye, and, microscopically, the ganglion-cells will be found to be almost completely atrophied, here and there one escaping, and a sclerotic patch consisting of proliferated neuroglia and connective tissue takes the place of the normal grey matter. Various consecutive changes follow; the anterior roots and nerve-trunks corresponding to the involved areas degenerate, the muscles supplied by them atrophy, and frequently the bones, vessels, and other structures also undergo atrophy. Occasionally there may be an ascending degeneration in the cord and atrophy of the corresponding motor region of the cerebral cortex.

The lesion is generally confined to one side of the cord, but involves several segments, and is more frequently situated in the dorso-lumbar than in the cervico-dorsal region.

There has been some controversy as to whether the changes first occur in the ganglion-cells or in the blood-vessels, but it is now generally accepted that the vascular changes are the primary ones.

According to Batten[1] the pathology of acute anterior poliomyelitis may be summarised as follows:

(1) The condition is due to a primary thrombosis of a branch or branches of the anterior spinal artery supplying the grey matter of the anterior horn.

(2) Such thrombosis may be produced by many and various forms of infection, and the disease is not due to a special specific infection.

The anatomical changes which occur in progressive muscular atrophy and bulbar paralysis are of much the same nature, but there is no evidence of inflammation, and these conditions will be described under the Primary Degenerations.

ACUTE ASCENDING PARALYSIS, or Landry's paralysis, probably includes several conditions of different ætiology, but all of toxic or infective origin, and characterised by an ascending paralysis without muscular atrophy, reaction of degeneration, or sensory disturbance. In some cases a poliomyelitis has been found to be present, in others a peripheral neuritis. Staphylococci and streptococci have been isolated. In a case examined by F. Buzzard[2] a coccus was isolated from the blood and cord which produced a rapidly-spreading palsy on sub-dural inoculation into a rabbit.

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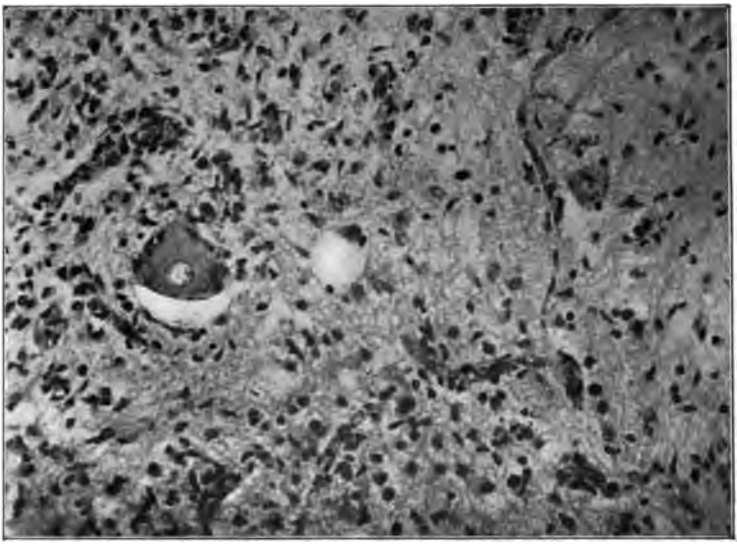
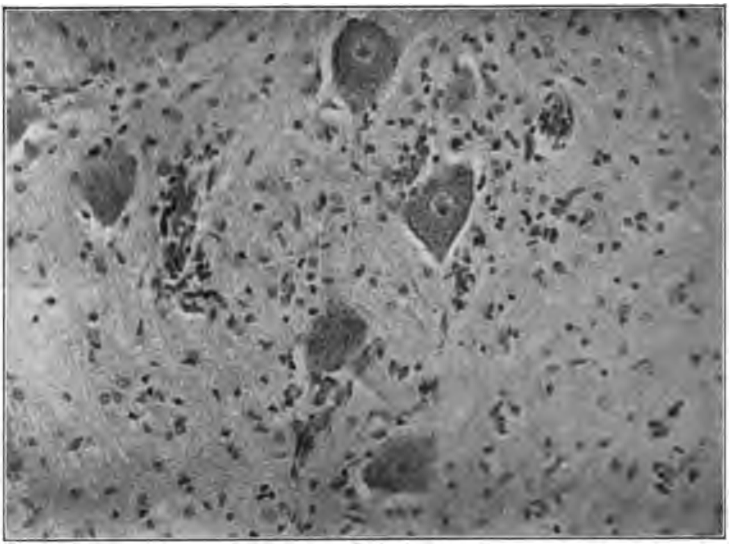
[1] *Brain*, vol. xxvii, 1904, p. 376.

[2] *Brain*, vol. xxvi, 1903, p. 94 (review).



A. Acute anterior poliomyelitis. Compare with B, and note destruction of nerve-cells, swelling, vacuolation, and disappearance of the Nissl granules in the nerve-cell remaining, and multiplication of nuclei. (Acid fuchsin, × 150.)



B. The unaffected side of the same cord as A. Note the numerous nerve-cells with their Nissl granules. (Acid fuchsin, × 150.)

Primary Degenerations of the Cord.

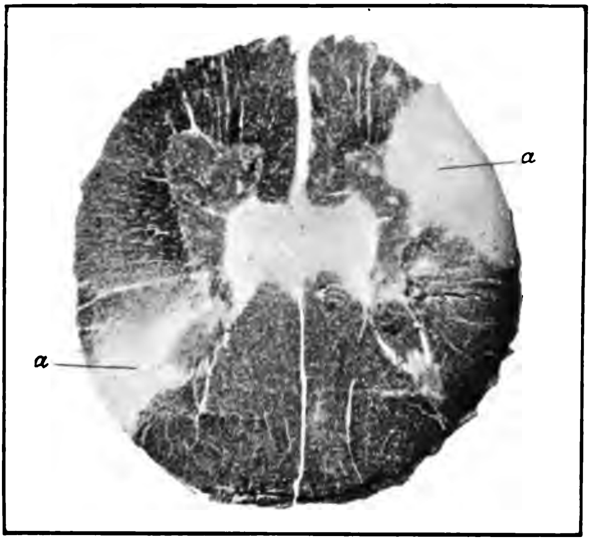
There is a class of diseases of the spinal cord characterised by more or less complete destruction (by sclerosis) of certain tracts or systems of fibres or groups of ganglion-cells, limited to the particular tracts involved, but continuous throughout these, in which there are no inflammatory or other causes to account for the lesions; their ætiology is still uncertain. These conditions are known as primary degenerations or primary system diseases; occasionally two or more tracts of different function are involved, and the condition is then known as a *combined system disease*. Such system diseases must be distinguished from the *secondary* ascending and descending degenerations which are consecutive to a transverse lesion of the cord, and which are also confined to definite tracts as already described. The essential changes in sclerosis are degeneration of the medullary sheaths of the white fibres, the myelin breaking up and disintegrating, swelling and degeneration of the axis cylinders, accumulation of fat granules in the part, and proliferation and hyperplasia of the neuroglia, and thickening of the vessel walls.

PRIMARY LATERAL SCLEROSIS is a condition in which the sclerosis is limited to the crossed pyramidal tracts of the lateral columns, giving rise to the condition which has been termed "spastic paraplegia" (spastic spinal paralysis). Frequently the direct cerebellar tract and posterior vesicular columns may also be involved. Some have denied the existence of this form of sclerosis, considering that the cases should be classed under the next variety.

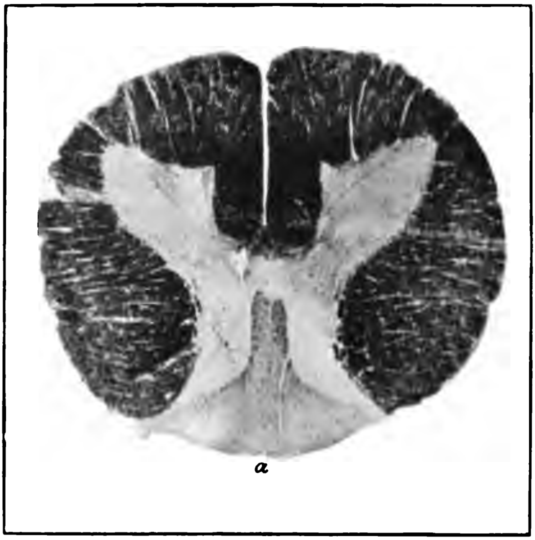
AMYOTROPHIC LATERAL SCLEROSIS is essentially a degeneration of the crossed and direct pyramidal tracts, together with atrophy of the ganglion-cells of the anterior cornua, and degeneration of the fibres of the anterior roots and sometimes of the peripheral nerves. The changes frequently extend into the medulla, and involve the hypoglossal nucleus and often the hypoglossal and glossopharyngeal nerves, and occasionally as far as the internal capsule. In consequence of the degeneration of the ganglion-cells, atrophy of the muscles ensues. Charcot and many other neuro-pathologists have regarded this disease as a primary one of the pyramidal tracts, with secondary involvement of the anterior cornua, and this view accords well with the facts. Others, however (*e.g.* Gowers), have suggested that it is a progressive muscular atrophy, with secondary changes in the peripheral, and then in the central motor, neurone. The cause is unknown.

Posterior sclerosis is the basis of the disease known as locomotor ataxy, or tabes dorsalis. In early cases the changes may be slight, but in advanced ones the white matter between the posterior roots is shrunken, and often appears darker than normal, and the pia between the posterior roots is frequently thickened and opaque. Microscopically, in advanced and well-marked cases, the whole of the posterior columns, with the exception of a patch immediately behind the posterior commissure (anterior root zone), is degenerate and sclerotic (Pl. XXVIII., B.); this includes the zone of Lissauer, and the columns of Burdach and of Goll (enumerated from the lateral columns to the posterior median fissure). The distribution of these changes varies greatly in different cases, at different stages, and at different levels; they are generally more marked in the lumbar or dorso-lumbar than in the cervical region. In the early stages the zone of Lissauer is principally affected, then the column of Burdach, and lastly the column of Goll, the two sides of the cord being involved

PLATE XXVIII.



A. Multiple sclerosis. *a, a.* Patches of sclerosis (also at centre). (Weigert-Pal method, × 6.)



P. Tabes dorsalis. The whole of the posterior columns (*a*) is degenerate. (Weigert-Pal method, × 6.)

To face page 506.

symmetrically. In the cervical region the degeneration is frequently confined to two small strips external to the columns of Goll and of Lissauer, but the posterior border of Goll's column or even the whole posterior column may be involved. In the dorsal cord the changes are more marked towards the posterior median fissure, while in the lumbar region they may be more pronounced in the columns of Lissauer and of Burdach than in those of Goll. More often than not the neuroglia is not increased, but the disappearance of medullated fibres gives an aspect of sclerosis to the affected area. The grey matter of the cord is practically unaffected. The cells of the ganglia of the posterior spinal roots are probably generally degenerate, and the same is perhaps true of the peripheral, sensory, and motor nerves.

Syphilis is now regarded as the principal ætiological factor in the causation of the disease.

The pathogenesis of tabes is still involved in much uncertainty. It was formerly regarded as a sclerosis of the posterior column—*i. e.* a primary system disease of the cord. At present the view most widely held is that it is a disease of the primary sensory neurone, the changes in the cord being therefore of the nature of a secondary ascending degeneration. On this conception the disease would not strictly be a primary system disease of the cord. A third theory holds that there is a syphilitic lepto-meningitis involving the posterior spinal roots, with subsequent degeneration, but in the majority of the cases no trace of such meningitis is to be found.

Hereditary spinal ataxia, or Friedreich's ataxia, is a disease characterised by ataxia, and is markedly hereditary and runs in families. Degeneration of the posterior and lateral columns is present, generally complete in the column of Goll and in the crossed pyramidal tract, while the column of Burdach and the direct pyramidal tract to a large extent escape. There is some increase in the neuroglia, and often atrophy of the posterior roots and of the peripheral nerves, and thickening of the pia. The cord is less than the normal size, particularly in the cervical region, and the cerebellum is often small (an hereditary cerebellar ataxia has been described). The nature of the disease is uncertain; one view is that it is a hypoplasia, or maldevelopment of the third primary vesicle of the neural canal (*i. e.* of the medulla, cerebellum, and cord); but since it is not evident in infancy, is progressive, and neuroglial hyperplasia is present, this theory does not seem to accord with the facts.

Progressive muscular atrophy includes several distinct affections. In the ordinary form (progressive spinal, Aran-Duchenne type) the muscles of the thenar and hypothenar eminences and the interossei first suffer, followed by atrophy of certain of the shoulder muscles. The changes in the cord are atrophy of the ganglion-cells, which may almost disappear, of the anterior cornua, particularly in the cervical region, and degeneration of the crossed pyramidal tract. There is no shrinkage of the grey matter, its contour remains unaltered; this is in great contrast to what occurs in anterior poliomyelitis, the chronic form of which progressive muscular atrophy greatly resembles. The anterior roots and peripheral motor nerves are also more or less degenerate, and the muscles supplied by them profoundly atrophied. Should the motor nuclei of the medulla become early involved, the type of disease assumes that which has been termed "bulbar" paralysis (glosso-labio-laryngeal paralysis). Somewhat similar conditions also occur in early childhood—(*a*) of the type just described, (*b*) attacking the lower extremity, descending spinal, and (*c*) a bulbar type. All of these diseases are regarded as being due to a primary spinal degeneration.

In contradistinction to these there are the *primary muscular dystrophies*, or *myopathies*, dependent probably on primary lesions of the muscles or peripheral motor nerves, which include the pseudo-hypertrophic paralysis, the juvenile form of progressive muscular atrophy of Erb, the Landouzy-Dejerine type, in which the face and shoulder-girdle are attacked, and the peroneal type of Tooth. It is unlikely that these have all the same genesis. In the pseudo-hypertrophic form the muscles may be the primary seat of disease; there is both atrophy and hypertrophy of the fibres in the affected muscles, hyperplasia of the connective tissue between the muscle-fibres and deposition of fat, and thickening of the coats of the blood-vessels. *The muscle-fibres always retain their transverse striation.*

In the peroneal type a chronic progressive interstitial neuritis has been most constantly found.

Erb has suggested that the trophic centres are the seat of functional disturbance, and hence atrophy is induced. Another theory suggests that a developmental weakness is present, owing to which the muscles attain only a certain stage of development, and when this is reached degeneration sets in.

In *myasthenia gravis* practically nothing has been detected in the nervous system. The only common lesion is scattered foci of lymphocytic extravasations in the voluntary muscles.[1]

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[1] See F. Buzzard, *Path. Soc. Trans.*, lvi, 1905, p. 355.

Degenerations of the Cord associated with Infections and Toxæmias.

Lesions of the cord may occur in pernicious anæmia, tuberculosis, and diabetes, also in ergotism and pellagra, in diphtheria and other infections, and in certain forms of poisoning.

In *pernicious anæmia* degeneration of the posterior and lateral columns is frequently present; in *tuberculosis* and *diabetes* the degeneration is, as a rule, confined to the posterior columns. In *ergotism* and *pellagra* (due to consumption of maize affected with fungoid disease) the lesions are much the same as in tabes, the columns of Burdach being affected primarily and those of Goll being spared or secondarily involved. *Diphtheria toxin* attacks the ganglion cells of the anterior horns and the peripheral nerves, while *streptococcus toxin* has an affinity for the posterior columns and roots. The lesions of *hydrophobia* have already been referred to (p. 502). *Lead, arsenic, alcohol, strychnine,* and other poisons may attack the cells of the anterior cornua and spinal ganglia.

The Peripheral Nerves.

The *ganglia* of the cranial nerves may be involved by extension from neighbouring lesions—*e. g.* disease of bone, etc. In trifacial neuralgia the Gasserian ganglion has been found to be more or less degenerate and sclerotic.

The *spinal ganglia* may be similarly involved by extension. Occasionally degenerative changes are met with in tabes, and have also been noted in cases of herpes zoster. The cervical ganglia, particularly of the pneumogastric, show changes in hydrophobia.

DEGENERATION and ATROPHY of nerves may result from inflammation, pressure, injury, especially division, or be secondary to disease of their nuclei of origin.

NEURITIS, inflammation, may be acute or chronic, and *parenchymatous,* when the nerve-tissue proper is primarily or principally involved, or *interstitial,* when the lesion is primarily one of the blood-vessels and supporting framework; generally there is more or less combination of the two. If several nerves are involved, the condition is termed a *polyneuritis.*

Interstitial neuritis is frequently seen after injury, chill (as in facial paralysis), accompanying gout, or as a result of surrounding disease. The nerve is swollen and pinkish in colour, the blood-vessels are dilated, and the connective tissue is infiltrated with round cells and proliferating. The myelin sheath and axis cylinder become secondarily involved and degenerate.

Parenchymatous neuritis is generally the result of a toxæmia, and is caused by diphtheria, and occasionally by other infective diseases, by beri-beri, alcohol, and mineral poisons, especially lead, arsenic, and mercury. The naked-eye changes may be scarcely noticeable, but, microscopically, the myelin may be swollen or fragmented, the axis cylinder swollen or beaded, and the nuclei of the sheath more numerous than normal. Secondary interstitial changes are frequent. In diphtheria interstitial changes predominate, in alcoholism and beri-beri the axis cylinder is early and markedly affected, in lead-poisoning the myelin sheaths are particularly involved, the axis cylinder remaining unaltered for a long time, in arsenic poisoning the whole nerve is involved. Tuberculous neuritis is a typical parenchymatous inflammation; in leprosy the lesion is mainly interstitial, in syphilis the blood-vessels are generally primarily affected. Diabetes and other cachectic states may be accompanied by a neuritis which is mainly parenchymatous.

Tumours of nerves are usually neuromata (p. 44) or sarcomata.

CHAPTER XIX.

DISEASES OF THE BONES AND JOINTS, TENDONS AND BURSÆ —DISEASES OF THE VOLUNTARY MUSCLES.

The bone-marrow.—In the young child the marrow of all the bones is of the red or lymphoid variety; in the adult only the short and flat bones contain this form of marrow. In pernicious anæmia much of the yellow or fatty marrow may be re-converted into red marrow. In myelogenous leukæmia the marrow is hyperplastic and the myelocytes are increased; in lymphatic leukæmia the marrow is also hyperplastic and crowded with lymphocytes.

Repair of fractures.—Immediately after the fracture, more or less hæmorrhage surrounds the ends of the fragments and infiltrates the adjacent tissues, which are torn and lacerated. A moderate degree of inflammatory exudation and of cellular infiltration ensue, which subside in the course of a few days, provided infection does not occur. Within two or three days proliferative changes are noticed in the cells of the periosteum, medulla, surrounding fibrous tissues, and vascular endothelium, which result in the production of a mass of granulation tissue between and around the ends of the fragments. The formative tissue so generated is known as *callus*; that produced by the periosteum around the fragments is the *external callus,* that between the ends is the *intermediary callus* and is also derived from the periosteum, while that derived from the osteoblasts of the medulla is known as the *myelogenic callus,* which is small in amount. By the end of the first week the inner layers of the periosteal callus have become differentiated into cartilage and osteogenetic tissue. The osteoblasts lay down a homogeneous or fibrillated ground substance, which soon becomes calcified, and a cancellous bony mass is formed and increases in amount for two or three weeks. A certain amount of *parosteal* or *provisional callus* is also developed from the surrounding connective tissues for four or five weeks and serves as a splint to keep the fragments in position. At the end of the seventh week all the callus is completely ossified, but consists of a soft cancellous bony tissue, which gradually becomes more compact, and the definitive callus is formed. This, too, undergoes changes which tend to reconstruct and reproduce the original bony structure of the part. The mass of external callus gradually becomes absorbed, and, if the ends of the fragments are in apposition, the medullary canal is restored, and little may ultimately remain of the callus. If, however, there has been dislocation or comminution of the fragments, a large amount of new bone may remain to weld together the fragments, and in the case of the forearm and leg may extend to the other bone and produce a *synostosis*.

Failure of bony union may occur from severe injury to the ends of the fragments, from pieces of the soft tissues intervening, or from movement, and in such cases a *pseudarthosis*, or false joint, may be formed by rounding of the ends of the fragments and the development of a fibrous capsule around them.

Passive hyperæmia of bone occurs in general venous obstruction and obstruction in neighbouring veins—*e. g.* in the skull in thrombosis of the sinuses. It seems to cause increased formation of bone, as in the clubbed fingers of chronic pulmonary and cardiac diseases.

Hæmorrhage occurs in traumatism, tumours, infective conditions, purpura, and scurvy. In infantile scurvy (Barlow's disease) numerous subperiosteal and endosteal hæmorrhages are present.

Thrombosis and *embolism* occasionally occur.

Atrophy of bone may result from inflammation, pressure, and inactivity, and in certain general states, senility, marasmus, osteomalacia, rickets, etc.

Hypertrophy and *hyperplasia* occur also as a result of hyperæmia and inflammation, and in acromegaly, etc.

Necrosis may ensue from injury, periosteitis, and osteomyelitis, and from thrombosis or embolism of the end arteries of the epiphyses. Phosphorus necrosis of the jaw is an infective process. *Necrosis* is applied to the death of a considerable piece of bone, the dead portion being known as a *sequestrum*; *caries* implies the gradual molecular disintegration of bone.

PERIOSTEITIS may be simple, or infective and suppurative. A *simple periosteitis* may arise from chronic inflammation, and a considerable amount of fibrous hyperplasia, or the production of new bone, result.

Suppurative periosteitis may occur from traumatism, or may be hæmatogenous, streptococci or staphylococci being the usual infective agents.

Phosphorus necrosis is generally a chronic infective periosteitis of the jaw, originating from carious teeth.

OSTEOMYELITIS, inflammation of the medulla, is usually an acute infective process arising from hæmatogenous infection, as in the course of pyæmia, or from traumatism. The infecting organisms are generally the *M. pyogenes aureus* or *albus*. The bone-marrow is hyperæmic and often hæmorrhagic, infiltrated with inflammatory exudation and cells, and foci of suppuration form and may extend throughout the marrow. This may cause necrosis of the central portion of the bone, or may spread to the Haversian canals and periosteum and cause total necrosis.

RAREFYING OSTEITIS is characterised by the formation of a vascular granulation tissue in the medulla and Haversian canals, and the absorption and canalisation of the surrounding bone, which becomes soft and spongy.

CONDENSING OSTEITIS is usually secondary to adjacent inflammation and results in the formation of new and compact bone.

TUBERCULOSIS OF BONE AND JOINTS.—The disease usually attacks the short cancellous bones of the wrist, ankle, or vertebral column, and the ends of the long bones forming the knee, elbow, and hip-joints; the shafts of the long bones are hardly ever, and the flat bones practically never, affected. If the affected portion of the bone enters into the constitution of a joint, the synovial membrane, capsule, and surrounding fibrous structures usually become involved. The inner aspect of the synovial membrane is thickened and covered with a layer of jelly-like, fungating granulations, and the membrane itself is thickened and gelatinous, and contains numerous typical tubercles, but, in the later stages at any rate, tubercle bacilli may be difficult to demonstrate.

The soft parts may be extensively diseased before the cartilage becomes affected; but it too ulcerates, granulations project from the erosions, and tuberculous nodules develop in the bone; these tend to caseate and suppurate, and cavities form in the bone.

Primary tuberculosis of the bone is, perhaps, commoner than primary tuberculosis of the synovial membrane.

SYPHILIS OF BONE is occasionally congenital and may affect the junction of the diaphysis with epiphysis. The acquired disease is much commoner. It may be a periosteitis with fibroid thickening (*node*) common in the tibia, and this may become converted into a gumma and caseate, or an osteitis, which chiefly affects the cranial and nasal bones, occasionally the long bones. The latter commences as a periosteitis and gradually implicates the bone, which becomes dense, and the diploe, or the medullary canal in the long bones, becomes obliterated. An endarteritis attacks the vessels and necrosis ensues, the necrotic portion becomes infiltrated, ulceration follows, and thus considerable portions of the bone may be completely destroyed.

Syphilitic disease of joints is less common than that of bone. It may take the form of an acute serous arthritis, and simulate rheumatism,[1] or gummata may develop in the synovial membrane, or the joint may be implicated secondarily to syphilitic inflammation of the bone or periosteum.

Tumours of bone and joints.—The myeloid sarcoma is the commonest, growing from the medulla, but periosteal round- or spindle-celled sarcoma is not infrequent. The *myeloma* occurs in the marrow as nodules or diffuse infiltration consisting of wide blood-spaces surrounded with round cells, most of which are plasma-cells. It may be leukæmic, by some is regarded as a lymphosarcoma, but the exact nature is not yet known (the myeloid sarcoma is also sometimes termed a myeloma). Fibroma, chondroma, and osteoma are not uncommon. *Cysts* usually arise from softening of solid tumours, but echinococcus cysts may be met with, and dentigerous cysts occur in the jaws. Secondary sarcoma and carcinoma may develop in the bones.

ARTHRITIS, inflammation of a joint, may be acute or chronic, and usually commences in the synovia (*synovitis*), but all the structures may be involved, particularly in the later stages.

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[1] Hewlett, *Med. Magazine*, xiii, 1904, p. 267.

Acute serous arthritis is the form of inflammation that accompanies acute rheumatism. The synovia are red and swollen, and a serous exudation distends the joint cavity. In gonorrhœa a sub-acute form of this arthritis is common (*gonorrhœal rheumatism*). The ordinary "sprain" from an injury is also of this nature.

Purulent arthritis is infective, and occurs as a result of injury or in the course of pyæmia.

Gouty arthritis.—In this sodium biurate is deposited in the cartilages, ligaments, capsule, synovial membrane, and adjacent tissues in the form of granules and acicular crystals, and is accompanied with hyperæmia and inflammatory exudation. The deposition of salts is stated by Ebstein to take place in areas of necrosis. Between the attacks the hyperæmia and exudation disappear, but the articular cartilages may appear as if smeared with plaster of Paris. In long-standing cases the cartilages may be more or less disintegrated and the other joint structures become much thickened, while the deposition of the uratic salts may form nodules which ulcerate through the skin.

Senile joint changes (senile arthritis) are frequent, particularly in the hip-joint, and consist of fatty degeneration of the cells of the articular cartilages, and disintegration of the intercellular substance, so that erosion of the cartilages takes place, the bone becomes exposed, and, by friction, smooth and polished (*eburnation*).

ARTHRITIS DEFORMANS (rheumatoid arthritis, rheumatic gout) has probably nothing to do with either rheumatism or gout. The disease may assume a mono-articular or a poly-articular form, and it is not improbable that several different affections are grouped under it. It may be due to some infective agent, is met with in ancient races —*e. g.* the Egyptians—and in animals, and frequently attacks an injured joint. The cartilage cells at first undergo some proliferation, but soon degenerate, and the cartilage becomes softened and eroded, exposing the bone, but at the margins may become ossified, giving rise to irregular outgrowths. Proliferation also occurs in the capsule, ligaments, and synovial membrane, with fibrous hyperplasia and sometimes the development of islands of cartilage which may subsequently ossify, producing enlargement, distortion, and limitation of movement. Absorption of the exposed bone follows, with condensation and eburnation, and the head of the bone becomes shortened and its articular cup shallow. In the spinal column the disease leads to the condition which has been termed *spondylitis deformans.*

Loose cartilages in joints seem to be derived from portions of the synovial membrane, which frequently contains cartilage cells. The villi of the membrane become enlarged from inflammation, chondrification occurs, and the chondrified mass ultimately becomes separated. Occasionally portions of the joint cartilage may become detached as a result of traumatism.

Neuropathic arthropathy. — In some diseases of the nervous system, particularly tabes, extraordinary changes take place in certain joints, the knee and hip-joints especially. The course is usually rapid and painless, the onset often sudden. The joint becomes distended with fluid, all the structures become softened, the cartilage and bone absorbed, and the ligaments loosened and stretched, so that the limb may be flail-like or dislocation may occur. Later, regenerative changes may ensue, and the condition simulates arthritis deformans.

GIANTS[1] are usually acromegalic (*e.g.* the skeletons of Magrath, Trinity College Museum, Dublin, and of Byrne, Roy. Coll. of Surgeons Museum, London), but occasionally may be normal individuals (*e.g.* Freeman, Roy. Coll. of Surgeons Museum, London).[2] The latter form is explicable by continued growth, the result of delayed union of epiphyses and diaphyses.

DWARFS may also be pathological or normal, and are thus classified by Windle[3]—

A. PATHOLOGICAL:

1. *Rachitic:* very rare, perhaps non-existent.
2. *Osteomalacic:* also very rare.
3. *Cretinoid:* with thyroid deficient or absent.
4. *Chondrodystrophic* or *achondroplastic*, to which class many dwarfs belong. The condition is also met with amongst animals.

Pancreatic inadequacy is also believed to cause a type of infantilism (see p. 375).

B. TERATOLOGICAL:

1. *Phocomelic*, where some of the intermediate parts of the limbs are absent.
2. *Micromelic:* limbs complete but unduly small, merges into the class of
3. *Nanosomes*, or true dwarfs, which may be primordial or sexual—that is, small men and women; or infantile or asexual—that is, permanent children.

The Tendons and Bursæ.

Inflammation of tendon-sheaths (*tenosynovitis*) and of bursæ (*bursitis*) is usually traumatic. A chronic bursitis (*hygroma bursarum*) with much effusion is not infrequent in the bursæ over the patella (*housemaid's knee*), over the olecranon (*miner's elbow*), and over the ischial tuberosity (*weaver's bottom*).

Ganglion is a distension of the tendon sheaths, usually of the back of the hand or wrist, with a gelatinous material. It is generally regarded as being caused by a hernial protrusion of the tendon-sheath, but it may be a new formation.

Melon-seed bodies not infrequently occur in enlarged bursæ and ganglions. They may consist of fibrin or of fragments of cartilage, or may be derived from tuberculous or syphilitic granulation tissue.

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[1] See *Brit. Med. Journ.*, 1904, ii, p. 1379; also *ref.* 2.

[2] Shattock, *Path. Soc. Trans.*, l, 1899, p. 185.

[3] *Brit. Med. Journ.*, 1904, ii, p. 1380.

GENERAL DISEASES ASSOCIATED WITH CHANGES IN THE BONES.

Rickets is a disease of early life, especially during the first two years, and is caused by bad hygienic surroundings and errors in diet. It occasions characteristic deformities of the bones. The junction between epiphysis and diaphysis, particularly in the wrist and ankle-joints, becomes thickened and nodose, and a like condition is frequent at the junction of the ribs and their cartilages. The fontanelles are slow to close, and the cranial bones may remain thin and attenuated. The bones of the face remain small and undeveloped, while the head tends to be enlarged, and the teeth are slow to erupt. Owing to deficiency of lime-salts, the bones are soft and pliable and yield to pressure, and hence arises the bowing of the legs (*genu varum*) or knock-knee (*genu valgum*), according as the convexity is outwards or inwards. The arms, not being subjected to constant pressure, do not suffer so much as the legs, but they, too, may yield to some extent. The pelvis may become deformed, the sacrum being advanced and the antero-posterior or conjugate diameter diminished. The ribs, being unable to resist the negative pressure in the chest during inspiration, tend to recede laterally, while the sternum protrudes forwards (*pigeon-breast*). The curves of the spine become exaggerated, often to a considerable extent, resulting in spinal curvature—twisting or *scoliosis*, anterior curvature or *lordosis*, posterior curvature or *kyphosis*, or a combination of these. If the child rests on its head continuously, absorption of areas in the parietals or occiput may result, with the formation of apertures—*craniotabes*. Growth tends to be retarded and the stature to be stunted.

The essential changes in rickets are due to disturbance of normal ossification. At the lines of ossification the zone of proliferation is broader than normal, and the cartilage is swollen and soft; the line of calcification, instead of being linear, is irregular; the marrow is hyperæmic, and between the cartilage and the formed bone a layer of soft, fibrous, uncalcified osteoid tissue is present.

Microscopically, an excessive proliferation of cartilage cells can be made out and irregular islands of uncalcified or partially calcified osteoid tissue are present. The bones are light and easily broken, and deficient in earthy salts (the calcium salts may be reduced to half the normal). The condition is usually associated with gastro-intestinal disturbance, anæmia, a mononuclear leucocytosis, and splenic enlargement.

The pathology of the disease is still obscure. It is not due simply to deficiency of lime-salts in the diet, though this will induce softening of the bones. The real change is a disturbance of normal osteogenesis, due possibly to a toxæmia caused by abnormal metabolism, the result of vicious alimentation.

When the morbid process ceases the osteoid tissue undergoes calcification, and in course of time is replaced by new and normal bone.

OSTEOMALACHIA, mollities ossium, is a disease of adult life, usually occurring in pregnant women or multipara, and characterised by decalcification and softening of the bones. While usually progressive, and sometimes recurring with every successive pregnancy, it occasionally becomes arrested. The condition generally first affects the pelvic bones, which may become greatly deformed, and may attack the spine and base of the skull, but not as a rule the bones of the extremities. The histological changes are not known with certainty.

The ovaries have been observed to be enlarged and hyperæmic, and their removal has been stated to arrest the disease, which has, therefore, been regarded as an ovarian trophoneurosis.

Fragilitas ossium is a condition characterised by extreme brittleness of the bones, chiefly of the ribs, and must be distinguished from osteomalachia, and also from malignant bone-disease, which frequently induces spontaneous fracture. It is usually met with in old persons and in the inmates of lunatic asylums. The bones are excessively porous, the Haversian canals appear to be dilated, and the marrow is red and hyperæmic, very cellular, and poor in fat. The pathology of this condition is unknown.

Osteitis deformans, first described by Paget, occurs in persons past middle life, and is characterised by thickening of bones, increase in their normal curvatures, and deformity. The bones most affected are those of the lower extremity, the spine, the clavicles, and the calvaria. The condition appears to start with absorption and the bone becomes spongy and porous, but this is compensated by an overgrowth from the periosteum and medulla, so that great thickening ensues.

Leontiasis ossea, hyperostosis cranii, is another remarkable condition in which the bones of the face and cranium become enormously thickened and the fissures and foramina contracted or obliterated.

Hypertrophic pulmonary osteo-arthropathy is generally associated with pulmonary tuberculosis. The hands and feet are enlarged and spade-like, the terminal phalanges being club-shaped and the nails incurved, and the distal ends of the long bones of the extremities are also enlarged, but the skull and face are unaffected, distinguishing it from acromegaly. According to Marie, the disease may be regarded as being caused by toxic substances elaborated in the lungs, having a selective action on certain parts of the bones and inducing a proliferating and ossifying periosteitis; venous hyperæmia may also aid.

ACHONDROPLASIA,[1] chondrodystrophia fetalis, fetal rickets, is a disease resembling rickets in many particulars but differing essentially from the latter, particularly in that it is congenital and the characteristic features are noticeable directly the child is born. In this disease the head is increased in size, the frontal bone is prominent, the anterior fontanelle wide, and the bridge of the nose depressed. The long bones of the extremities are short and stunted, but the bone itself is thick and strong, the normal curves are exaggerated, especially in the case of the radius and tibia, and the ends of the diaphysis become expanded so as to fit in cup-like fashion over the epiphysis. The membrane bones, such as the clavicle, and the ribs, sternum, and vertebræ are unaffected, though there is usually lordosis and prominence of the sacral promontory. The hands are short and fat, the fingers of about the same length, tapering at their extremities and radiating from one another. Should the patient grow up his mental faculties are unimpaired—an important distinction from cretinism. A premature synostosis of the pre-sphenoid, basi-sphenoid, and basi-occipital is almost a constant feature in achondroplasia and leads to the prognathus and depressed bridge. The bones of the cranial vault are always expanded and thin. With regard to the deficiency of growth of the long bones, Barlow, in 1880, suggested two main causes—(1) the presence of a fibrous layer growing in from the periosteum between the diaphysis and epiphysis. This so-called "periosteal inclusion" was first mentioned by Urtel, Eberth, and others, and varies greatly in extent and thickness in the different cases, being visible microscopically only in some. Various suggestions have been offered as to its production, the two main theories being those of Urtel and Hoess on the one hand, and of Eberth on the other. The two former observers suggest that it is due to a relative greater production of periosteum as compared with enchondral growth, whilst Eberth believes that it is due to an overgrowth of the epiphysis beyond the peripheral diaphyseal line, caused by an involution of periosteum which subsequently proliferates. Although in some cases this inclusion may interfere with the normal growth of the bone, as it must have done in those instances in which it is found to be ossified, in others it is far too rudimentary to have done so; (2) an abnormal arrangement of the cartilage cells along the line of ossification. These cells have been shown to be large and spherical and lacking the usual arrangement into parallel rows. Kaufmann has divided these cases into three groups. In the first of these, to which he has given the title "chondrodystrophia fetalis hypoplastica," there is an inhibition of proliferation of the cartilage cells. In the second group, "chondrodystrophia fetalis hyperplastica," these cells are enormously increased in number and closely packed together, leading to enlargement of the epiphyseal cartilage; whilst in the third and rarest variety the cartilage is softened and growth irregular ("chondrodystrophia fetalis malica").

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[1] See Balme and Reid, *Practitioner*, December, 1904, p. 780.

Parrot considered that the deformity was due to the cartilages having lost their osteogenetic power (hence his name of "achondroplasia"), but subsequent writers have disagreed with this suggestion.

MYELOPATHIC ALBUMOSURIA[1] is a condition associated with anæmia, progressive weakness, and the discharge in the urine of a peculiar proteid allied to the albumoses (p. 403), and terminating fatally. Spontaneous fracture and deformity of the bones are frequent. The ribs, sternum, and vertebræ are always affected, occasionally other bones. The change in the bones is the formation of a gelatinous, soft, vascular new growth, probably sarcomatous, but characterised by the fact that several parts of the skeleton are simultaneously affected and that there is no tendency to metastasis. Microscopically, the growth consists of round cells, somewhat resembling lymphocytes, with little or no intercellular substance. The ætiology of the disease is unknown.

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[1] See Moffatt, *Lancet*, 1905, i, p. 207.

The Voluntary Muscles.

Simple atrophy occurs as a senile change and from disuse.

Neuropathic atrophy occurs when a muscle is separated from its trophic centre (the nerve-cells of the anterior horns of the spinal grey matter) and follows section or inflammation of a mixed nerve, or anterior poliomyelitis; it is most typically seen in the latter in infantile paralysis. *Progressive muscular atrophy* may be of the same nature, but chronic in course, though it is considered by some to be a primary disease of the muscles, with secondary degeneration of the spinal nerve-cells. In the juvenile forms and in the pseudo-hypertrophic paralysis the atrophy seems to be a primary one of the muscles. Microscopically, the muscle-fibres usually lose their striation and become fragmented, and coagulative necrosis and fatty degeneration may ensue, and the connective tissue between the fibres proliferates. In the pseudo-hypertrophic form there is a marked formation of adipose tissue, which increases the bulk of the muscle in spite of its atrophy, and the fibres which remain for the most part retain their striation (see also p. 508).

Cloudy swelling is frequent in fever and infective conditions. The muscle-fibres are swollen, their striations become indistinct or disappear, and they become granular.

Fatty degeneration occurs in neuropathic atrophy, in cachectic and toxæmic states, phosphorus poisoning, etc.

Coagulation necrosis, Zenker's degeneration, is characterised by loss of striation, swelling, and fragmentation into glassy masses. It occurs in typhoid and other infective conditions, and chiefly attacks the abdominal muscles, the psoas, and the adductors of the thighs (see also p. 20).

Myositis, inflammation, is generally secondary to inflammation of neighbouring structures or traumatic. *Purulent myositis* is infective.

Myositis ossificans is characterised by the formation of plates, nodules, or splinters of true bone in the muscles, generally of the arm or leg. It may follow inflammation or traumatism, but one form is progressive, and usually commences in early life, and ultimately may involve the majority of the voluntary muscles. The ætiology is unknown.

Tuberculosis of the muscles, as a primary affection, is rare. *Syphilis* may occur as a chronic interstitial inflammation, or in the form of gummata. *Glanders* is not infrequent in the form of multiple miliary abscesses. *Actinomycosis* may be met with. The *Trichina spiralis* (p. 152), *Cysticercus cellulosæ* (p. 146), are not infrequent, but echinococcus cysts are rare.

Tumours of muscle are usually round- or spindle-celled sarcomata. *Fibromata* may occur. *Carcinoma* is met with only as a secondary growth. *Teratomata* and *dermoid cyst* may occasionally occur.

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